Organizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

07-62231

SOLICITUD DE PATENTE DE INVENCIÓN

TÍTULO: DERIVADOS DE (3R,6R) -3- (2,3-DIHIDRO-1H-INDEN-2-IL)-2,5-PIPERAZINADIONA 1,6 SUSTITUIDA COMO ANTAGONISTAS DE RECEPTORES DE OXTOCINA PARA EL TRATAMIENTO DE TRABAJO DE PARTO PRE-TÉRMINO, DISMENORREA Y ENDOMETRIOSIS

SOLICITANTE: GLAXO GROUP LIMITED.

DIRECCIÓN Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra

A GLK 31496

APODERADO: J. IAN RAISBECK

BOGOTÁ, 2 de Junio de 2007

SDO 31/03/08

P2007/000368

-24

EXAMEN TECNICO DE FONDO

Nº Radicación	07-6773	Fecha de presentación	20.06.07
Nº Prioridad	GR 06 8773 6	Fecha de Prioridad	22.12.06

Palabras clave

D20 H27:09
G01-601/09

CLASIFICACIONES INTERNACIONALES DE BUSQUEDA

A61K 31/496			

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES

WO 06 67967			
Patente Original			

BASES DE DATOS CONSULTADAS

Epoline			
Espacenet			

INFORMES DE EXAMENES EN OTRAS OFICINAS

Oficina	Fecha	Reiv. afectadas

ANTERIORIDADES ENCONTRADAS

Documento	Relevancia	Reiv. afectadas
WO 03053967	Sin Int	1-9

LITERATURA NO PATENTES

Documento	Relevancia	Reiv. afectadas

Observaciones: Diferencial. Uso, Mod. Inal.

Fecha del examen: 16-02-09

Son Obs 1 a 3
04-03-2010

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-062231- -00000-0000
Fecha: 2007-06-20 16:42:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 349

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL **P2007/000088**

(1) **SOLICITUD DE:**

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: GLAXO GROUP LIMITED
Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN
Nacionalidad o Domicilio: BRITANICA
Lugar de Constitución: INGLATERRA
Teléfono: _____ Fax: _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

(3) **REPRESENTANTE O APODERADO**

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IDENTIFICACIÓN
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C.E. [ ] Otro [ ]
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Número 79.376.996 Btá
TP 135.799

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Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2005/005007 Fecha Diciembre 22, 2005

Publicación Internacional No. WO 2006/067462 Fecha Junio 29, 2006

(6) **Título (54)** DERIVADOS DE (3R,6R) - 3- (2,3- DIHIDRO- 1H- INDEN- 2- IL) - 2,5- PIPERAZINADIONA 1,6 SUSTITUIDA COMO ANTAGONISTAS DE RECEPTORES DE OXTOCINA PARA EL TRATAMIENTO DE TRABAJO DE PARTO PRE- TÉRMINO, DISMENORREA Y ENDOMETRIOSIS

(7) **Clasificación Internacional (51)** **C07D 241/08, A61P 15/06**

(8) **Prioridad**

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Diciembre 23, 2004	0428235.6

(9) **Comprobante de pago No.** **07 – 45.390** **Fecha** **5 de junio de 2007**

(10) **ANEXOS**

- [x] 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.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] 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.
- [x] Otros. Búsqueda Internacional

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

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Nacionalidad: Canadiense

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-062231- -00000-0000

Fecha: 2007-06-20 16:42:44 Dep. 2020 N'JECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 349

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 45,390
FECHA : JUNIO 5 DE 2007

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00110-6	67535363	05/06/2007	6,757,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

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

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

APOSTILLA

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

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

CERTIFICADO

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

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

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

Marlen Neira C

Como Notario Veintisiete de éste Círculo hago constar que ésta Fotocopia coincide con su original que he tenido a la vista.
15 MAR 2007

MARLEN NEIRA CASTR
Traductor e Intérpreie Ofi
Inglés - Español - Inglé
Resolución No. 2117 del 7 O

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

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 constituída 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 debiday 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 ece de agosto del año dos mil tres.

Como Notario Veintisiete de éste Círculo hago constar que esta Fotocopia coincide con su original que he tenido a la vista.
15 MAR 2007

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

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35 Piccadilly London W1J OLJ
Telephone:+44 (0)20 7208 2900 Facsimile: +44 (0)20 7208 0066 DX No. 48521 Piccadilly 2

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Como Notario Veintisiete de este Circulo
hago constar que ésta Fotocopia coincide
con su original que he tenido a la vista.
15 MAR 2007

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

Certified/Attesté

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**

FOREIGN AND COMMONWEALTH OFFICE
LONDON

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

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

7

OLARTERAISBECK

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Power of Attorney

The undersigned,

Glaxo Group Limited

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

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

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 Official

Date/Fecha: 13 August 2003

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

Como Notario Veintisiete de este Circuito hago constar que esta fotocopia coincide con su original que he tenido a la vista.

15 MAR 2007

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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PCT

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0428235.6 23 December 2004 (23.12.2004) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LEACH, Colin, Andrew** [GB/US]; GlaxoSmithKline, 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US). **LIDDLE, John** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **PEACE, Simon** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **PHILP, Joanne** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **SMITH, Ian, Edward, David** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **TERRELL, Lamont, Roscoe** [US/US]; GlaxoSmithKline, 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US). **ZHANG, Jing** [CN/US]; GlaxoSmithKline, 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US).

(74) Agent: **SARDHARWALA, Fatema**; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

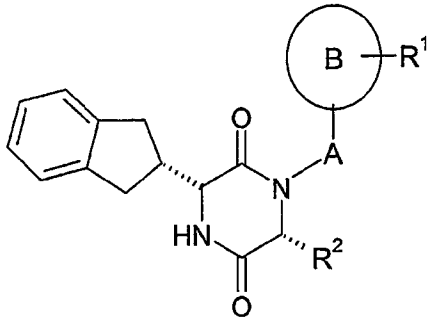
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 1,6 - SUBSTITUTED (3R,6R) -3- (2,3-DIHYDRO-1H-INDEN-2-YL)-2,5-PIPERAZINEDIONE DERIVATIVES AS OXYTOCIN RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PRE-TERM LABOUR, DYSMENORRHEA AND ENDOMETRIOSIS



(I)

(57) Abstract: The present invention relates to compound S of Formula (I).

WO 2006/067462 A1

9

1,6-SUBSTITUTED (3R,6R)-3-(2,3-DIHYDRO-1H-INDEN-2-YL)-2,5-PIPERAZINEDIONE DERIVATIVES AS OXYTOCIN RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PRE-TERM LABOUR, DYSMENORRHEA AND ENDOMETRIOSIS

FIELD OF THE INVENTION

This invention relates to novel diketopiperazine derivatives having a potent and selective antagonist action at the oxytocin receptor, to processes for their preparation, pharmaceutical compositions containing them and to their use in medicine.

BACKGROUND OF THE INVENTION

US5817751 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-bisphospate (FBPase).

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 oxapiperazinyl compounds that are inhibitors of Factor Xa.

WO03/053443 describes diketopiperazine derivatives which exhibit activity as selective antagonists at the oxytocin receptor.

WO2005/000840 describes diketopiperazine derivatives which exhibit activity as selective antagonists at the oxytocin receptor.

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).

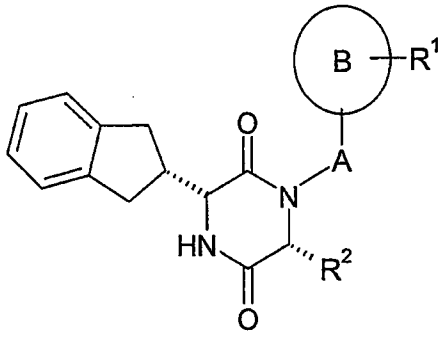
Pre-term births/labour (between 24 and 37 weeks) causes about 60% of infant mortality/morbidity and thus a compound which inhibits the uterine actions of oxytocin e.g. oxytocin antagonists, should be useful for the prevention or control of pre-term labour.

SUMMARY OF THE INVENTION

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

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides at least one chemical entity selected from a compound of Formula (I):



(I)

and physiologically acceptable derivatives thereof,

wherein:

A represents a C_{1-4}alkylene group optionally substituted by one or more C_{1-4}alkyl groups;

the ring B represents a mono-, bi- or tricyclic aryl or heteroaryl group containing one or more heteroatoms independently selected from O, S or N, wherein the aryl or heteroaryl group may be optionally substituted by one or more R^1 groups which may be independently selected from C_{1-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}cycloalkoxy, C_{1-6}alkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, -Oheterocyclyl, -Oheteroaryl, -$S(O)_n$heterocyclyl or -$S(O)_n$heteroaryl (each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or -NR^3R^4); or R^1 may additionally be independently selected from halo, hydroxyl, -NR^3R^4, nitro, cyano, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, carboxyl, -$CONR^3R^4$, -COR^5, -$S(O)_nR^6$, -NR^7COR^8, -$S(O)_mNR^9R^{10}$ or -$NR^{11}S(O)_mR^{12}$;

R^2 represents C_{3-7}alkyl, C_{3-7} cycloalkyl or phenyl, each of which may be further optionally substituted by one or more groups selected from C_{1-4}alkyl or C_{3-7} cycloalkyl;

R^3 and R^4 independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-3}alkoxyC_{1-6}alkyl, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, COR^5, heteroaryl, heterocyclyl, aryl or -$NR^{3a}R^{4a}$;

or R^3 and R^4, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or a 4- to 7-membered heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-NR^{3a}R^{4a}$, COR^5, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, COR^5, heteroaryl, heterocyclyl, aryl or $-NR^{3a}R^{4a}$);

R^{3a} and R^{4a} independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, or aryl;

or R^{3a} and R^{4a}, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or a 4- to 7-membered heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, or aryl);

R^5 represents C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-6}alkyl, aryl, heteroaryl or heterocyclyl, wherein the C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-6}alkyl, aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

R^6 represents C_{1-6}alkyl, C_{1-6}cycloalkyl, trifluoroC_{1-6}alkyl, aryl, heteroaryl, or heterocyclyl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, trifluoroC_{1-6}alkyl, aryl, heteroaryl, or heterocyclyl groups may be optionally substituted by one or more groups

independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-3}alkoxyC_{1-6}alkyl, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

R^7 represents H or C_{1-4}alkyl (optionally substituted by one or more groups independently selected from by halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$);

R_8 represents C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

or R^7 and R^8 together with the interconnecting atoms to which they are attached form a 4- to 7-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein the heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

R^9 and R^{10} independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl group may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, , aryl, $-NR^3R^4$ or heterocyclyl optionally substituted with C_{1-6}alkyl;

or R^9 and R^{10}, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or a 4- to 7-membered heterocyclyl ring which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-NR^3R^4$, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$);

R^{11} represents H or C_{1-4}alkyl (optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$);

R^{12} represents C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

or R^{11} and R^{12} together with the interconnecting atoms to which they are attached form a 4- to 7-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein the heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

n represents 0, 1 or 2;

and m represents 1 or 2.

In one aspect of the invention there is provided at least one chemical entity comprising a compound of Formula (IA) and physiologically acceptable derivatives thereof, wherein the compound of Formula (IA) is a compound of Formula (I) which is other than a compound selected from List 1:

List 1

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(2-pyridinyl)ethyl]-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(4-nitrophenyl)ethyl]-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(4-pyridinyl)ethyl]-2,5-piperazinedione

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-(4-pyridinylmethyl)-2,5-piperazinedione;

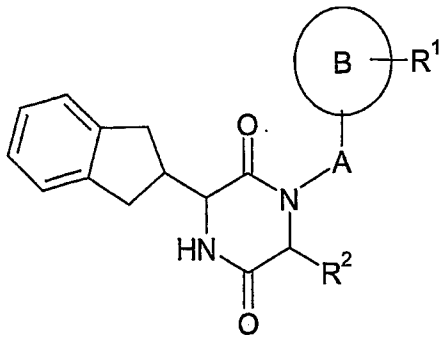
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-1-yl)ethyl]-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[6-(trifluoromethyl)-3-pyridinyl]methyl}-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[2-(1-methyl-1*H*-imidazol-2-yl)ethyl]-6-(2-methylpropyl)-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(3-pyridinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[2-(1-methyl-1*H*-imidazol-5-yl)ethyl]-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{2-[4-(methylsulfonyl)phenyl]-ethyl}-2,5-piperazinedione;
N-(3-{2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]ethyl}phenyl)methanesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(2-methyl-2*H*-tetrazol-5-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1-ethyl-5-methyl-1*H*-pyrazol-4-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1-ethyl-1*H*-pyrazol-4-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({4-[(dimethylamino)methyl]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-{[3,5-bis(trifluoromethyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-6-cyclopropyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methylphenyl)methyl]-6-phenyl-2,5-piperazinedione; and
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]sulfinyl}phenyl)-methyl]-6-(1-ethylpropyl)-2,5-piperazinedione.

In an alternative embodiment of the invention there is provided at least one chemical entity selected from a compound of Formula (A):



(A)

and physiologically acceptable derivatives, salts, solvates and prodrugs thereof,

wherein:

A represents a C_{1-4}alkylene group optionally substituted by one or more C_{1-4}alkyl groups;

the ring B represents a mono-, bi- or tricyclic aryl or heteroaryl group containing one or more heteroatoms independently selected from O, S or N, wherein the aryl or heteroaryl group may be optionally substituted by one or more R^1 groups which may be independently selected from C_{1-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}cycloalkoxy, C_{1-6}alkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, -Oheterocyclyl, -Oheteroaryl, -$S(O)_n$heterocyclyl or -$S(O)_n$heteroaryl (each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4); or R^1 may additionally be independently selected from H, halo, -NR^3R^4, nitro, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, carboxyl, -$CONR^3R^4$, -COR^5, -$S(O)_nR^6$, -NR^7COR^8, -$S(O)_mNR^9R^{10}$ or -$NR^{11}S(O)_mR^{12}$;

R^2 represents C_{3-7}alkyl, C_{3-7} cycloalkyl or phenyl, each of which may be further optionally substituted by one or more groups selected from C_{1-4}alkyl or C_{3-7} cycloalkyl;

R^3 and R^4 independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or the group –$NR^{3a}R^{4a}$;

or R^3 and R^4, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$NR^{3a}R^{4a}$, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group –$NR^{3a}R^{4a}$);

R^{3a} and R^{4a} independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocyclyl, or aryl;

or R^{3a} and R^{4a}, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$NR^{3a}R^{4a}$, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, or aryl);

R^5 represents H, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-6}alkyl, aryl, heteroaryl or heterocyclyl, wherein the C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-6}alkyl, aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4;

R^6 represents H, C_{1-6}alkyl, C_{1-6}cycloalkyl, trifluoroC_{1-6}alkyl, aryl, heteroaryl, or heterocyclyl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, trifluoroC_{1-6}alkyl, aryl, heteroaryl, or heterocyclyl groups may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4;

R^7 represents H or C_{1-4}alkyl (optionally substituted one or more groups independently selected from by halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4);

R_8 represents C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4;

or R^7 and R^8 together with the interconnecting atoms to which they are attached form a 5- or 6-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4;

R^9 and R^{10} independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl group may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4;

or R^9 and R^{10}, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or heterocyclyl ring which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -NR^3R^4, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4);

R^{11} represents H or C_{1-4}alkyl (optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4);

R^{12} represents C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4;

or R^{11} and R^{12} together with the interconnecting atoms to which they are attached form a 5- or 6-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein the heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocycyl, aryl or the group -NR^3R^4;

n represents 0, 1 or 2;

and m represents 1 or 2.

In one aspect of the invention there is provided at least one chemical entity comprising a compound of Formula (A') and physiologically acceptable derivatives thereof, wherein the compound of Formula (A') is a compound of Formula (A) which is other than a compound selected from List 1 as hereinbefore defined.

Certain compounds of Formula (I) or Formula (A) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by Formula (I) or Formula (A) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of Formula (I) or Formula (A) may exist in tautomeric forms other than that shown in the Formula and these are also included within the scope of the present invention.

The compounds of Formula (I) or Formula (A) wherein at least one of the groups R_1 or R_2 contains a basic or acidic grouping may form salts with physiologically acceptable acids or bases and reference to compounds of Formula (I) or Formula (A) herein includes such salts.

Terms and Definitions

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) or Formula (A), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of Formula (I) or Formula (A), or an active metabolite

or residue thereof. Preferred pharmaceutically acceptable derivatives are salts and solvates.

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-(acetyloxy)ethyl esters.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl.

As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy.

As used herein, the term "alkylene" as a group or a part of a group refers to a linear or branched saturated hydrocarbon linker group containing the indicated number of carbon atoms. Examples of such groups include methylene, ethylene and the like.

As used herein, the term "aralkyl" as a group or a part of a group refers to an alkyl group as herein defined which contains the indicated number of carbon atoms, the alkyl group being substituted with an aryl group as herein defined.

As used herein, the term "cycloalkyl" as a group or a part of a group refers to a saturated cyclic hydrocarbon group of 3 to 7 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups.

As used herein, the term "cycloalkyloxy" as a group or a part of a group refers to an -O-cycloalkyl group wherein cycloalkyl is as herein defined.

As used herein, the term "halogen" or halo refers to fluorine, chlorine, bromine or iodine.

As used herein, the term "aryl" refers to refers to a cyclic compound made up of one or more benzene rings and includes phenyl, naphthyl, phenanthrenyl and anthracenyl, each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$.

As used herein, the term "heteroaryl" as a group or a part of a group refers to an optionally substituted aromatic group comprising one to four heteroatoms selected from N, O and S, the aromatic group containing one, two or three 5- or 6- membered conjugated or fused rings with at least one ring having a conjugated pi-electron system. Heteroaryl groups may be substituted by one or more groups independently selected from halo, oxo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$. Examples of such 5-membered heteroaryl groups include furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl or tetrazolyl and these heterocycles may be substituted as described above. Examples of 6-membered heteroaryl groups include pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl and these heterocycles may be substituted as described above. Examples of fused heteroaryl groups, include benzimidazolyl, benzofuranyl, indolyl, indazolyl, benzoxazolyl, naphthyridinyl, pteridinyl, quinolinyl and these heteroaryl groups may be substituted as described above.

As used herein, the term "heterocyclyl" as a group or a part of a group refers to an optionally substituted, 3- to 7-membered, saturated or partially saturated cyclic hydrocarbon group containing one to four heteroatoms selected from N, O and S. Heterocyclyl groups may be substituted by one or more groups independently selected from halo, oxo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$. Examples of 5-membered heterocyclyl groups include pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, each of which may be substituted as described above. Examples of 6-membered heterocyclyl groups include pyranyl, morpholino, thiomorpholino, piperidinyl, each of which may be substituted as described above. An example of 7-membered heterocyclyl groups includes homopiperazine (hexahydro-1*H*-1,4-diazepin-1-yl). In addition, the term "heterocyclyl" includes fused heterocyclyl groups, for example benzopiperidinyl, benzopiperazinyl, each of which may be substituted as described above.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

For the avoidance of doubt, the term "independently" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. Indeed, in certain embodiments of the invention, pharmaceutically acceptable salts of the compounds according to Formula (I) or Formula (A) may be preferred over the respective free base or free acid because such salts impart greater stability or solubility to the molecule thereby facilitating formulation into a dosage form. Accordingly, the invention is further directed to pharmaceutically acceptable salts of the compounds according to Formula (I) or Formula (A).

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. For a review on suitable salts see Berge et al, J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, sulfamic, nitric, phosphoric, succinic, maleic, hydroxymaleic, acrylic, formic, acetic, hydroxyacetic, phenylacetic, butyric, isobutyric, propionic, fumaric, citric, tartaric, lactic, mandelic, benzoic, o-acetoxybenzoic, chlorobenzoic, methylbenzoic, dinitrobenzoic, hydroxybenzoic, methoxybenzoic salicylic, glutamaic, stearic, ascorbic, palmitic, oleic, pyruvic, pamoic, malonic, lauric, glutaric aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, naphthalenesulfonic (e.g. 2-naphthalenesulfonic), p-aminobenzenesulfonic (i.e. sulfanilic), hexanoic, heptanoic, or phthalic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, hydroiodide, sulfate, bisulfate, nitrate, phosphate, hydrogen phosphate, succinate, maleate, malate, formate, acetate, trifluoroacetate, saccharate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2- naphthalenesulfonate), methanesulphonic,

ethanesulphonic, p-toluenesulphonic, isethionate or hexanoate salt. In one embodiment there is provided the formate and hydrochloride salts of the compounds of the invention.

A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base (e.g. ammonia, triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration. Pharmaceutically acceptable base salts include ammonium salts and salts with organic bases, including salts of primary, secondary and tertiary amines, including aliphatic amines, aromatic amines, aliphatic diamines, and hydroxy alkylamines, such as methylamine, ethylamine, isopropylamine, diethylamine, ethylenediamine, ethanolamine, trimethylamine, dicyclohexyl amine, diethanolamine, cyclohexylamine and N-methyl-D-glucamine. Other suitable pharmaceutically acceptable base salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as hydroxides, carbonates and bicarbonates of sodium, potassium, lithium, calcium, magnesium, aluminium, and zinc; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the compound of Formula (I) or Formula (A).

Other non-pharmaceutically acceptable salts, for example oxalates may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of Formula (I).

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I) or Formula (A) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water and the solvate may also be referred to as a hydrate.

In one aspect of the invention A represents CH_2, $CH(CH_3)$ or CH_2CH_2. In another aspect, A represents CH_2 or $CH(CH_3)$. In a further aspect, A represents CH_2.

In one aspect of the invention the ring B represents phenyl, pyridyl, pyrimidinyl, quinolinyl or pyrazolyl. In another aspect the ring B represents phenyl, pyridyl, pyrimidinyl or pyrazolyl. In a further aspect, the ring B represents phenyl.

In one aspect, the ring B is optionally substituted by one or two R^1 groups. In another aspect, R^1 groups may be independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, (each of which may be optionally substituted by one or more groups independently selected from hydroxyl, C_{1-6}alkyl, C_{1-6}alkoxy, heterocyclyl, aryl or $-NR^3R^4$); or R^1 may additionally be independently selected from halo, hydroxyl, $-NR^3R^4$, nitro, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, carboxyl, $-CONR^3R^4$, $-COR^5$, $-S(O)_nR^6$, $-NR^7COR^8$, $-S(O)_mNR^9R^{10}$ or $-NR^{11}S(O)_mR^{12}$. In another aspect, R^1 groups may be may be independently selected from C_{1-6}alkyl, heteroaryl, for example pyrazolyl, (each of which may be optionally substituted by one or more groups independently selected from C_{1-6}alkoxy or $-NR^3R^4$); or R^1 may additionally be independently selected from $-NR^3R^4$, $-CONR^3R^4$, $-S(O)_nR^6$, $-NR^7COR^8$ or $-S(O)_mNR^9R^{10}$.

In one aspect of the invention R^2 represents C_{3-5}alkyl, or R^2 represents C_{3-5}cycloalkyl which may be further optionally substituted by C_{1-2}alkyl, wherein the total number of carbon atoms in the R^2 group is between 3 and 5.

In one aspect of the invention R^3 and R^4 independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, heterocyclyl or heteroaryl groups may be further optionally substituted by one or more groups independently selected from hydroxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-3}alkoxyC_{1-6}alkyl, heterocyclyl, aryl or $-NR^{3a}R^{4a}$; or R^3 and R^4, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N (for example morpholine or piperazine); and wherein the 5- or 6-membered heterocyclyl ring may be further optionally substituted by C_{1-4}alkyl, (wherein the C_{1-4}alkyl group may be further optionally substituted by one or more groups independently selected from heterocyclyl or aryl). In another aspect R^3 and R^4 independently represent H or C_{1-4}alkyl which is optionally substituted by one or more groups independently selected from hydroxyl, C_{1-2}alkyl or $-NR^{3a}R^{4a}$, or R^3 and R^4, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N (for example morpholine or piperazine); and wherein the 5- or 6-membered heterocyclyl ring may be further optionally substituted by C_{1-4}alkyl.

In one aspect of the invention R^{3a} and R^{4a} independently represent H or C_{1-6}alkyl. In another aspect R^{3a} and R^{4a} independently represent C_{1-6}alkyl.

In one aspect of the invention R^5 represents C_{1-6}alkoxy which is optionally substituted with hydroxyl, C_{1-6}alkoxy, or $-NR^3R^4$ (for example NMe_2, morpholine, piperidine, piperazine or pyrrolidine). In another aspect R^5 respesents C_{1-3}alkoxy.

In one aspect of the invention R^6 represents C_{1-6}alkyl, trifluoroC_{1-6}alkyl or heterocyclyl, each of which may be optionally substituted by one or more groups independently selected from C_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, heterocyclyl or $-NR^3R^4$ (for example NMe_2, morpholine, piperidine or piperazine). In another aspect R6 represents C_{1-3}alkyl.

In one aspect of the invention R^7 represents H or C_{1-4}alkyl.

In one aspect of the invention R_8 represents C_{1-6}alkyl or heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from C_{1-6}alkyl, or $-NR^3R^4$.

In one aspect of the invention R^9 and R^{10} independently represent H, C_{1-6}alkyl, heterocyclyl or heteroaryl each of which is optionally substituted by one or more groups independently selected from hydroxyl, carboxyl, C_{1-6}alkyl, aryl $-NR^3R^4$ or heterocyclyl optionally substituted by C_{1-6}alkyl, or R^9 and R^{10}, together with the interconnecting N-atom to which they are attached form a 5-, 6- or 7-membered heterocyclyl ring which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N (for example morpholine, piperidine or piperazine); and wherein the 5-, 6- or 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, or $-NR^3R^4$, (wherein the C_{1-4}alkyl group may be further optionally substituted by C_{1-6}alkoxy). In another aspect R^9 and R^{10} both represent CH_3, or R^9 and R^{10}, together with the interconnecting N-atom to which they are attached form a morpholine, piperidine, piperazine or pyrrolidine ring.

In one aspect of the invention R^{11} represents H or C_{1-4}alkyl. In another aspect of the invention R^{12} represents C_{1-6}alkyl. In a further aspect R^{11} and R^{12} together with the interconnecting atoms to which they are attached form a 5- or 6-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein the heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$.

In one aspect of the invention n represents 2.

In one aspect of the invention m represents 2.

In one aspect of the invention, for compounds of Formula (A), the stereochemistry of the two chiral centres on the central piperazine-2,5-dione ring is (3*R*, 6*R*).

It is to be understood that the present invention covers all combinations of aspects of the invention, including suitable, convenient and preferred groups, described hereinabove.

In one aspect, chemical entities useful in the present invention may be chosen from at least one chemical entity of Formula (I) selected from the group consisting of:

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2(hydroxymethyl)benzyl]-piperazine-2,5-dione;
methyl 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(methyloxy)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-methylphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methyloxy)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methyloxy)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(trifluoromethyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-methylphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-[(3-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-fluorophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(1-piperidinylmethyl)-phenyl]methyl}-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[2-(dimethylamino)ethyl]oxy}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-fluorophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(3-fluorophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(trifluoromethyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(trifluoromethyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(trifluoromethyl)oxy]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({3-[(trifluoromethyl)oxy]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2,6-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2,6-dichlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-pyridinylmethyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2,2-dimethylpropyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1R)-1-phenylethyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2,6-dimethyl-3-pyridinyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2,4-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-bromophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethyl-benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-hydroxyphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(3-nitrophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(2-nitrophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-({3-[(difluoromethyl)oxy]phenyl}methyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-[(3-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(3,4-dichlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-{[3,5-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(trifluoromethyl)oxy]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3,5-dimethylphenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(phenylmethyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(4-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[3-(2-pyridinyloxy)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-6-cyclohexyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylphenyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-6-(dicyclopropylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2,2-dimethylpropyl)-1-{[2-(methylsulfonyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(trifluoromethyl)-sulfonyl]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methyloxy)-4-(methylsulfonyl)phenyl]-methyl}-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methyloxy)-4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2-chloro-4-(methylsulfonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(1,1-dimethylethyl)thio]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(methylsulfonyl)-2-pyridinyl]methyl}-2,5-piperazinedione ;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-nitrobenzyl)piperazine-2,5-dione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-(1-methyl-4-piperidinyl)benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[4-(dimethylamino)-1-piperidinyl]-carbonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(1-methyl-4-piperidinyl)benzamide formate;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[3-(dimethylamino)propyl]-*N*-methylbenzamide formate;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[3-(dimethylamino)propyl]benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methyl-1-piperazinyl)-carbonyl]phenyl}methyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(4-morpholinyl)ethyl]benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(2-hydroxyethyl)benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(2-hydroxyethyl)-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;

2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-4-piperidinylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1-piperazinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(dimethylamino)methyl]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzenesulfonamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethyl-propyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethyl-benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylsulfonyl)-phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzene-sulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methyl-1-piperazinyl)-sulfonyl]phenyl}-methyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(1-methyl-4-piperidinyl)-benzenesulfonamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethyl-propyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-(1-methyl-4-piperidinyl)benzenesulfonamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(4-morpholinyl)ethyl]benzene-sulfonamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]-benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(4-ethyl-1-piperazinyl)sulfonyl]phenyl}-methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-({4-[2-(methyloxy)ethyl]-1-piperazinyl}sulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1-piperazinylsulfonyl)-phenyl]methyl}-2,5-piperazinedione hydrochloride;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylthio)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylsulfonyl)-phenyl]methyl}-2,5-piperazinedione hydrochloride;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-({1-[2-(methyloxy)-ethyl]-4-piperidinyl}sulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-{[3-(4-morpholinyl)propyl]-thio}phenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-{[3-(4-morpholinyl)propyl]-sulfonyl}phenyl)methyl]-2,5-piperazinedione;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]thio}phenyl)-methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methyl-4-piperidinyl)-thio]phenyl}methyl)-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methyl-4-piperidinyl)-sulfonyl]phenyl}methyl)-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(1-ethyl-4-piperidinyl)sulfonyl]phenyl}-methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-Aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)methanesulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)ethane-sulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-2-propanesulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-*N*-methylmethanesulfonamide ;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(1,1-dioxido-2-isothiazolidinyl)phenyl]-methyl}-6-(1-ethylpropyl)-2,5-piperazinedione;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)acetamide;
N^1-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-N^3,N^3-dimethyl-ß-alaninamide formate;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-phenyl)-4-(dimethyl-amino)butanamide formate;
(formic acid - *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-1-methyl-4-piperidinecarboxamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(2-oxo-1-pyrrolidinyl)-phenyl]methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzenesulfonamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-{[ethyl(methyl)amino]methyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[1-(3-methylphenyl)-1*H*-pyrazol-4-yl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(3-pyridinyl)ethyl]-2,5-piperazinedione;

N-(3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)methanesulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-*N*-methylacetamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{2-[4-(methyloxy)-3-(methylsulfonyl)phenyl]-ethyl}-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1*S*)-1-phenylethyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(3-pyridinylmethyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(4-pyridinylmethyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1,1-dimethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-oxo-1,2-dihydro-3-pyridinyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-hydroxyphenyl)methyl]-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[1-(phenylmethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-6-cyclopentyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylthio)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylthio)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2,4-dichlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-(2-biphenylylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2-(3-pyridinyl)ethyl]-2,5-piperazinedione;
(3*R*,6*R*)-6-(dicyclopropylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methylphenyl)-methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(4-{[2-(dimethylamino)ethyl]oxy}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(1-pyrrolidinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
formic acid - (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({3-[(dimethylamino)methyl]-phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione (1:1);
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione;
N-cyclopropyl-4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[3-(3-pyridinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-fluoro-2-(hydroxymethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(2-pyrazinylamino)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(2-pyrimidinylamino)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(2-pyrimidinylamino)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(1-methyl-1*H*-imidazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({4-[(1-methyl-1*H*-imidazol-2-yl)amino]phenyl}-methyl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-({4-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(5-methyl-1,3-thiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-({4-[(5-methyl-1,3-thiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-pyrazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-1,2,3-triazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(1*H*-tetrazol-1-yl)phenyl]methyl}-2,5-piperazinedione;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1*H*-tetrazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-5-fluorobenzoic acid;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-fluoro-*N*,*N*-dimethylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-fluoro-2-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-5-fluoro-*N*-(2-hydroxyethyl)benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzamide;
3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;
3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(2-hydroxyethyl)benzamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-[2-(methyloxy)ethyl]benzamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide;

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4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({4-[(4-methyl-1-piperazinyl)carbonyl]-phenyl}methyl)-6-(2-methylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-{1-[2-(methyloxy)ethyl]-4-piperidinyl}benzamide;
(3*R*,6*R*)-1-{[2,4-bis(hydroxymethyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylthio)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2,4-bis(1-pyrrolidinylcarbonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2,4-bis(4-morpholinylcarbonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*,*N*',*N*'-tetramethyl-1,3-benzenedicarboxamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*'-bis(2-hydroxyethyl)-*N*,*N*'-dimethyl-1,3-benzenedicarboxamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*'-bis[2-(dimethylamino)ethyl]-*N*,*N*'-dimethyl-1,3-benzenedicarboxamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*'-dimethyl-*N*,*N*'-bis[2-(methyloxy)ethyl]-1,3-benzenedicarboxamide;
(3*R*,6*R*)-1-({2,4-bis[(4-methyl-1-piperazinyl)carbonyl]phenyl}methyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)-2-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-[(4-methyl-1-piperazinyl)-carbonyl]-4-(methylsulfonyl) phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-[2-(methyloxy)ethyl]-5-(methylsulfonyl)benzamide;
N-[2-(diethylamino)ethyl]-2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-5-(methylsulfonyl)benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-(methylsulfonyl)-2-{[(2*S*)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl}phenyl)methyl]-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methylhexahydro-1*H*-1,4-diazepin-1-yl)sulfonyl]phenyl}methyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-{[(2*R*)-1-ethyl-2-pyrrolidinyl]methyl}benzenesulfonamide;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[(3*S*)-3-(dimethylamino)-1-pyrrolidinyl]-sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[(3*R*)-3-(dimethylamino)-1-pyrrolidinyl]-sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-2,5-dioxo-1-piperazinyl]-methyl}benzenesulfonamide;
N-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)sulfonyl]glycine;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methylethyl)sulfonyl]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
formic acid - *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-N^2,N^2-dimethylglycinamide (1:1);
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1*H*-imidazol-1-yl)phenyl]-methyl}-2,5-piperazinedione;
formic acid - (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]-sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione (1:1);
(3*R*,6*R*)-6-cyclopentyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[4-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1*H*-pyrazol-1-yl)phenyl]-methyl}-2,5-piperazinedione;
and physiologically acceptable derivatives thereof.

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

Thus, compounds of Formula (I) or Formula (A) 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, 1993 (30) pp129-142. 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) pp1301-1305.

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, endometriosis and benign prostatic hyperplasia.

The compounds may also be useful to delay labour prior to elective caesarean section or transfer of the patient to a tertiary care centre, treatment of sexual dysfunction (male and female), particularly premature ejaculation, obesity, eating disorders, congestive heart failure, arterial hypertension, liver cirrhosis, nephritic or ocular hypertension, obsessive-compulsive disorder and neuropsychiatric disorders. The compounds of the invention may also be useful for improving fertility rates in animals, e.g. farm animals.

The invention therefore provides for the use of at least one chemical entity comprising a compound of Formula (IA) or Formula (A') and physiologically acceptable derivatives thereof for use in therapy and in particular use as medicine for antagonising the effects of oxytocin upon the oxytocin receptor and for use in the treatment or prevention of diseases or conditions mediated through the action of oxytocin.

The invention also provides for the use of at least one chemical entity comprising a compound of Formula (IA) or Formula (A') and physiologically acceptable derivatives thereof in the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor. In one embodiment, the invention provides for the use of at least one chemical entity comprising a compound of Formula (IA) or Formula (A') and physiologically acceptable derivatives thereof in the manufacture of a medicament for the treatment of one or more diseases or conditions selected from pre-term labour, dysmenorrhea and endometriosis.

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 at least one chemical entity comprising at least one chemical entity comprising a compound of Formula (IA) or Formula (A') and physiologically acceptable derivatives thereof.

According to another aspect, the invention also provides for a method of treating or preventing diseases or conditions mediated through the action of oxytocin, which comprises administering to a mammal in need thereof an effective amount of at least one chemical entity comprising a compound of Formula (IA) or Formula (A') and

physiologically acceptable derivatives thereof. In one aspect, the disease or condition is selected from pre-term labour, dysmenorrhea and endometriosis.

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.

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.

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.

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.

Compositions

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.

The invention thus further provides a pharmaceutical composition comprising at least one chemical entity comprising a compound of Formula (IA) or Formula (A') and physiologically acceptable derivatives thereof and a pharmaceutically acceptable carrier or diluent. The formulation may optionally contain 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.

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

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, microcystalline 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.

Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

Pharmacy Examples

Tablets

a)	Compound of the invention	50.0mg
	Lactose	70.0mg
	Microcrystalline Cellulose	70.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Compression weight	200.0mg

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.

b)	Compound of the invention	50.0mg
	Lactose	120.0mg
	Pregelatinised Starch	20.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	2.0mg
	Compression weight	200.0mg

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

a)	Compound of the invention	50.0mg
	Lactose	148.0mg
	Magnesium Stearate	2.0mg
	Fill weight	200.0mg

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.

b)	Compound of the invention	50.0mg
	Lactose	132.0mg
	Polyvinylpyrrolidone	8.0mg

Cross-linked polyvinylpyrrolidone	8.0mg
Magnesium Stearate	2.0mg
Fill weight	200.0mg

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.

Injection Formulation

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

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) or Formula (A). 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.

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.

The compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

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When a compound of the invention or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will 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 and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. The compounds of the present invention may be used in combination with tocolytics or prophylactic medicines. These include, but are not limited to, beta-agonists such as terbutaline or ritodrine, calcium channel blockers, e.g. nifedepine, non-steroidal anti-inflammatory drugs, such as indomethacin, salts of magnesium, such as magnesium sulphate, other oxytocin antagonists, such as atosiban, and progesterone agonists and formulations. In addition the compounds of the present invention may be used in combination with antenatal steroids including betamethasone and dexamethasone, prenatal vitamins especially folate supplements, antibiotics, including but not limited to ampicillin, amoxicillin/clavulanate, metronidazole, clindamycin, and anxiolytics.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

When administration is sequential, either the compound of the present invention or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

Abbreviations

In describing the invention, chemical elements are identified in accordance with the Periodic Table of the Elements. Abbreviations and symbols utilized herein are in accordance with the common usage of such abbreviations and symbols by those skilled in the chemical arts. The following abbreviations are used herein:

BOC	tert-butyloxycarbonyl
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform

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DCM	dichloromethane
DIPEA	diisopropylamine
dioxan	1,4-dioxan
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d6	deuterated dimethylsulfoxide
EDC.HCl	1-(3-dimethylaminopropyl)-3-ethylcarboiimide hydrochloride
ES+ MS	Positive Electrospray mass spectrometry
h	hours
ES- MS	Negative Electrospray mass spectrometry
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HPLC	high pressure liquid chromatography
LCMS	Liquid Chromatography Mass Spectrometry
mesylate	methylsulfonate
min	minutes
NMP	N-methylpyrrolidone
NMR	Nuclear Magnetic Resonance spectroscopy
Pd/C	palladium on carbon
Rt	retention time
RT	room temperature
SPE	solid phase extraction
TBDMSO	tert-butyldimethylsilyloxy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tosylate	4-toluenesulfonate
xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Compound Preparation

Compounds of the invention may be prepared, in known manner in a variety of ways. In the following reaction Schemes and hereafter, unless otherwise stated R^1 to R^{12}, A, n and m are as defined above for Formula (I) or Formula (A), and the ring B represents a mono-, bi- or tricyclic aryl or heteroaryl group containing one or more heteroatoms independently selected from O, S or N, for example a phenyl, pyrazole or pyridinyl ring. These processes form further aspects of the invention.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV), etc, with the exception of Formula (A). Subsets of compounds of Formulae (I) and (A) are defined as (Ia), (Aa), (Ib), (Ab), (Ic), (Ac), (Id), (Ad), (Ie), (Ae), (If), (Af), (Ig), (Ag), (If), (Af), (Ii), (Ai), (Ij), (Aj), (Ik), (Ak), (Im), (Am), (In), (An), (Io), (Ao), (Ip), (Ap), (Iq) and (Aq).

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Compounds of Formula (I) or Formula (A), may be prepared according to the general reaction Scheme 1 by the following steps as indicated in the Scheme:

Step (a)

A reaction between a chiral N-protected carboxylic acid of Formula (II), wherein P represents a suitable nitrogen protecting group, for example alkoxycarbonyl (e.g. *tert*-butoxycarbonyl), or Cbz; a suitable amine of Formula (III), an aldehyde (IV) and an isonitrile (V), wherein J is an optional substituent, for example, J is a chloro, benzyloxy or TBDMSO substituent or is absent, in a suitable solvent such as methanol, trifluoroethanol or chloroform, to give compounds of Formula (VI), wherein J is an optional substituent, for example, J is a chloro, benzyloxy or TBDMSO substituent or is absent.

It will be apparent to the person skilled in the art that compounds of Formula (II), (III), (IV) and (V) may be added together in varying order, for example an imine may be formed between aldehyde (IV) and amine (III) before the addition of carboxylic acid (II) and isonitrile (IV), or the reagents may be added together in a "one-pot" mixture.

It will be further apparent to the skilled person that the amine (III) may be added to the reaction in the form of a salt, such as a hydrochloride salt; in such a case a base may be added to the reaction mixture, for example triethylamine or DIPEA.

Step (b)

A deprotection reaction to remove nitrogen protecting group P from compounds of Formula (VI) to provide compounds of Formula (VII), wherein J is an optional substituent, for example, J is a chloro, benzyloxy or TBDMSO substituent or is absent. When P is an alkoxycarbonyl group (e.g. *tert*-butoxycarbonyl), deprotection may be carried out using a suitable acid, for example TFA or HCl in a suitable solvent such as 1,4-dioxan or methanol, or in the presence of acetyl chloride in methanol. When P is a Cbz group, deprotection may be carried out by hydrogenation in the presence of a suitable catalyst, for example Pd/C, in a suitable solvent such as acetic acid or methanol.

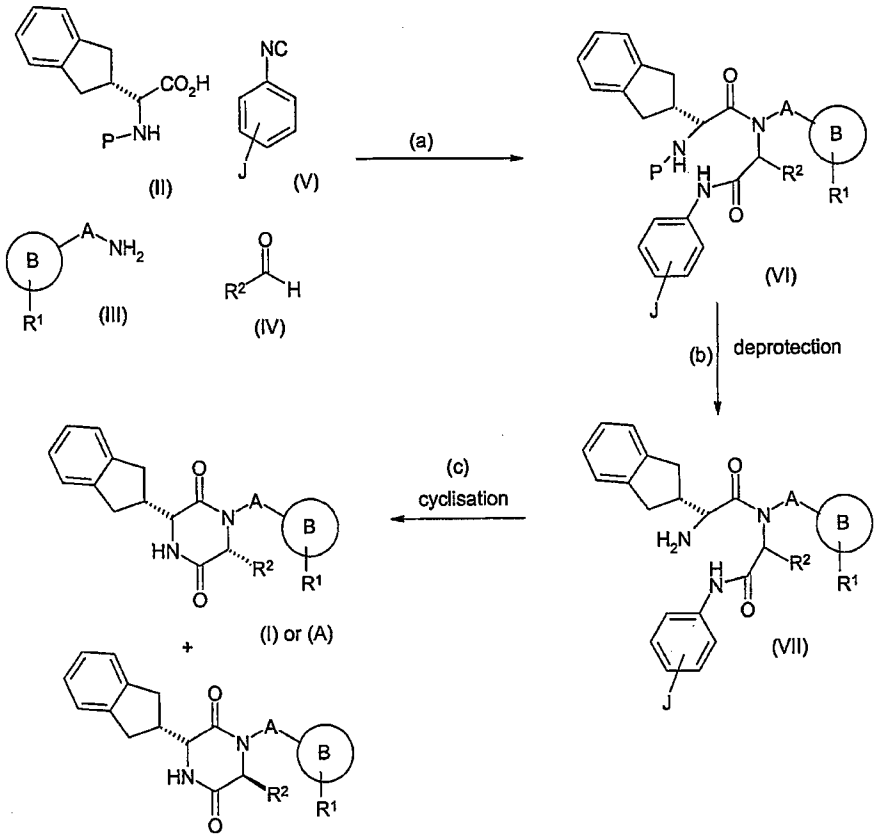
Step (c)

A cyclisation reaction of compounds of Formula (VII) to provide compounds of Formula (I) or Formula (A). Cyclisation may be carried out in the presence of a suitable acid such as glacial acetic acid, in a suitable solvent such as chloroform. Alternatively, cyclisation may be carried out in the presence of a suitable base, such as sodium bicarbonate, or a mixture of sodium bicarbonate and triethylamine. Alternatively, cyclisation may be carried out in the absence of acid or base in a suitable solvent.

It will be apparent to the person skilled in the art that the cis-diastereoisomer, i.e. the compound of Formula (I) or Formula (A), may be separated from the trans diastereoisomer (both isomers shown in Scheme 1) by conventional purification

techniques, for example by chromatography. Alternatively, the mixture of cis- and trans-diastereoisomers may be subjected to functional group interconversion(s), for example those depicted in the reaction Schemes 3 to 12 hereinbelow, and separated by conventional techniques thereafter.

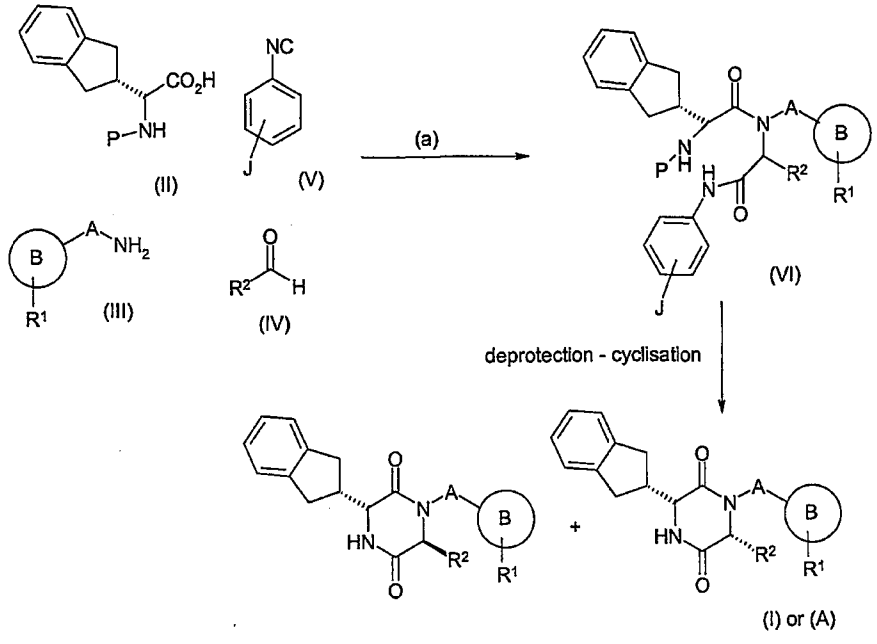
Scheme 1



Alternatively, when P is an alkoxycarbonyl group (e.g. *tert*-butoxycarbonyl), the deprotection step and the cyclisation step may be carried out in a one-step reaction as shown in Scheme 2, in the presence of a suitable acid, for example HCl, in a suitable solvent, for example a mixture of 1,4-dioxan and DCM.

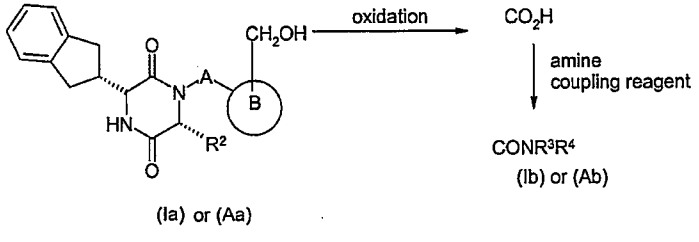
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Scheme 2



Compounds of Formula (Ib) or Formula (Ab), wherein R^1 represents $-CONR^3R^4$, may be prepared from compounds of Formula (Ia) or Formula (Aa), wherein R^1 represents $-CH_2OH$, according to reaction Scheme 3. Compounds (Ia) or (Aa) may be oxidised at the R^1 position to the carboxylic acid group $-CO_2H$. This can be carried out for example in a two-step process by reacting compounds of Formula (Ia) or (Aa) with 4-methylmorpholine N-oxide (NMNO) with tetrapropylammonium perruthenate (TPAP) in a suitable solvent such as dichloromethane, followed by oxidation of the resulting aldehyde using a suitable oxidising agent, such as sodium chlorite, to provide the carboxylic acid. The carboxylic acid may then be reacted with a suitable amine HNR^3R^4, for example in the presence of a coupling agent, such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in the presence of a suitable base such as triethylamine, in a solvent e.g. dichloromethane, to form the compounds of Formula (Ib) or Formula (Ab).

Scheme 3

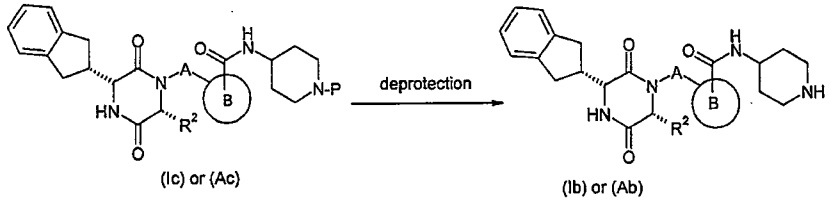


Compounds of Formula (Ib) or Formula (Ab), wherein R^1 represents the group $-CONR^3R^4$, wherein either one of R^3 or R^4 represents a group which contains an NH

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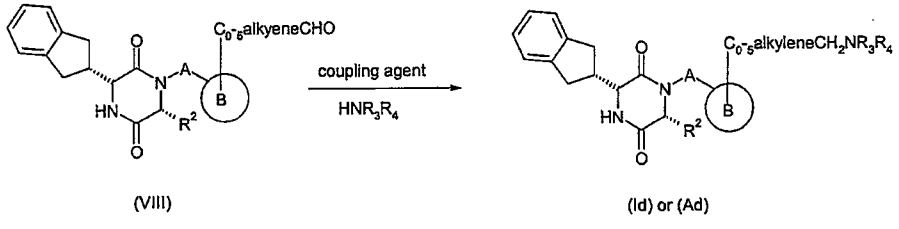
moiety, for example a nitrogen-containing heterocyclyl group, e.g. piperidine, may be prepared according to reaction Scheme 4 (piperidine shown by way of example) by deprotecting the corresponding N-protected compound of Formula (Ic) or (Ac), wherein P is a suitable nitrogen protecting group. Where P is, for example, an alkoxycarbonyl group (e.g. *tert*-butoxycarbonyl), deprotection may be carried out in the presence of an acid, e.g. HCl, in a suitable solvent such as 1,4-dioxan.

Scheme 4



Compounds of Formula (Id) or (Ad), wherein R^1 represents C_{1-6}alkyl substituted by the group $-NR^3R^4$ may be prepared according to reaction Scheme 5 by reacting an aldehyde compound of Formula (VIII) with a suitable coupling agent, such as sodium triacetoxyborohydride, in the presence of a suitable amine HNR^3R^4.

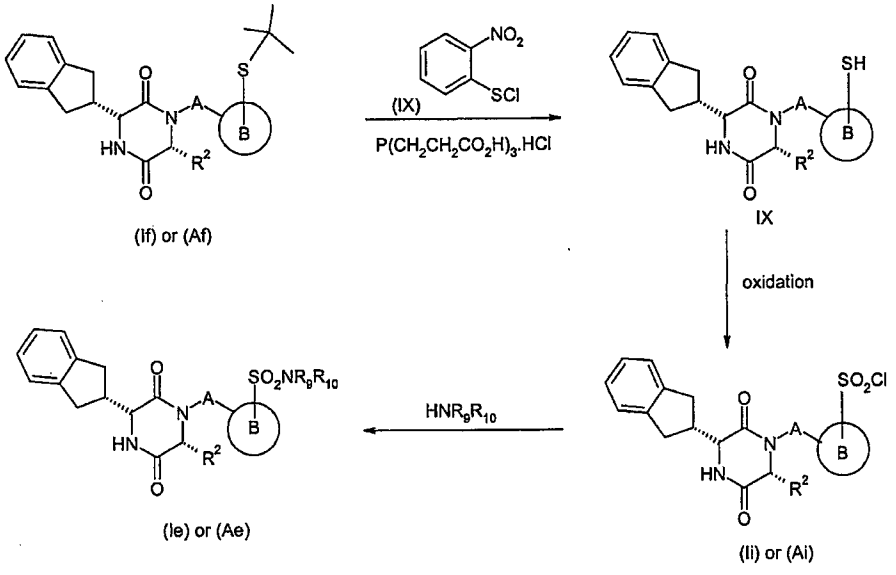
Scheme 5



Compounds of Formula (Ie) or Formula (Ae), wherein R^1 represents the group $-S(O)_mNR^9R^{10}$ may be prepared according to reaction Scheme 6 by deprotecting sulfanyl compounds of Formula (If) or (Af) to form the thiol compound IX. This may be carried out for example using a nitroaryl sulfenyl chloride, for example 2-nitrobenzenesulfenyl chloride, in the presence of a suitable base, such as triethylamine, and a suitable solvent, for example DMF, and tris(carboxyethyl)phosphine hydrochloride. Compound IX may be oxidised, e.g. with sulfuryl chloride in the presence of a suitable base, such as potassium nitrate, to form a sulfonyl chloride compound of Formula (Ii) or (Ai) which is subsequently reacted with a suitable amine HNR^9R^{10} to form the amide (Ie) or (Ae).

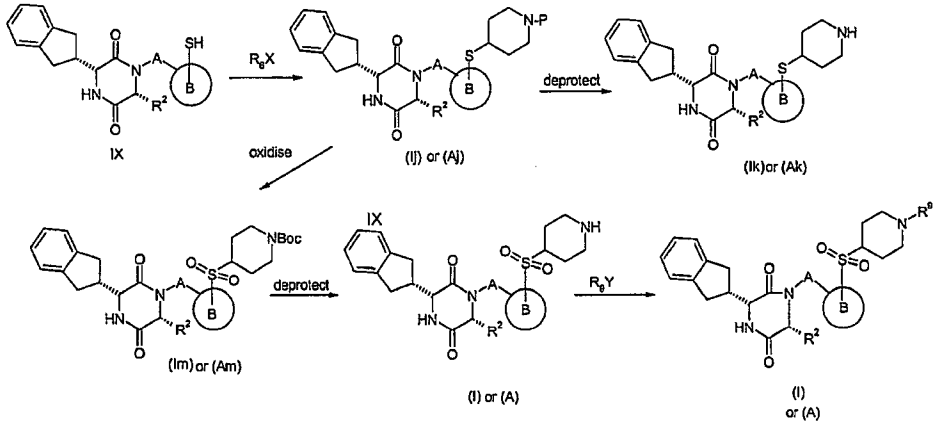
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Scheme 6



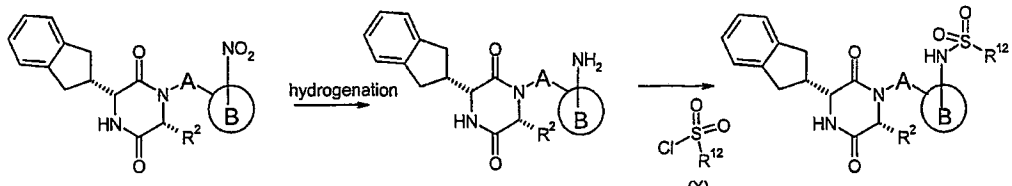
Compounds of Formula (I) or Formula (A), wherein R^1 represents the group $-S(O)_nR^6$ may be prepared according to reaction Scheme 7 starting from the thiol compound of Formula IX. This may be reacted with a suitable N-protected amine R^6X, wherein X is a suitable leaving group, for example mesylate, tosylate or halo, to form a sulfanyl compound of Formula (Ij) or (Aj), wherein P is a suitable nitrogen protecting group, which can either be oxidised to the sulfone (Im) or (Am) using a suitable oxidising agent such as 3-chloroperoxybenzoic acid, or simply deprotected, for example using an acid, where P is a *tert*-butoxycarbonyl group, to form a sulfanyl compound of Formula (Ik) or (Ak). The sulfone (Im) or (Am) may be deprotected, for example using an acid, where P is a *tert*-butoxycarbonyl group, and may be further modified, if desired, to introduce a suitable group R^9 on the amine, by treatment with R^9Y, wherein Y is a suitable leaving group, for example mesylate, tosylate or halo, in the presence of a suitable base, for example potassium carbonate, in a suitable solvent, such as DMF.

Scheme 7



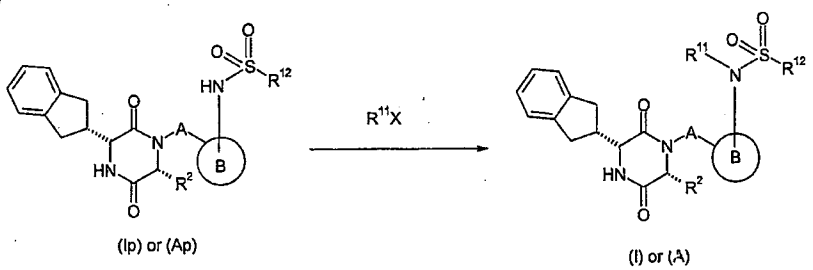
Compounds of Formula (I) or Formula (A), wherein R^1 represents the group $-NR^{11}S(O)_mR^{12}$, wherein R^{11} represents H, may be prepared according to reaction Scheme 8 starting from the nitro compound (In) or (An) which may be hydrogenated using standard conditions, for example in the presence of a Pd/C catalyst, to form the amine (Io) or (Ao) which may be reacted with a suitable sulfonyl chloride compound of Formula (X) in the presence of a suitable base, such as triethylamine and dimethylaminopyridine, to form the sulphonamide compound (Ip) or (Ap).

Scheme 8



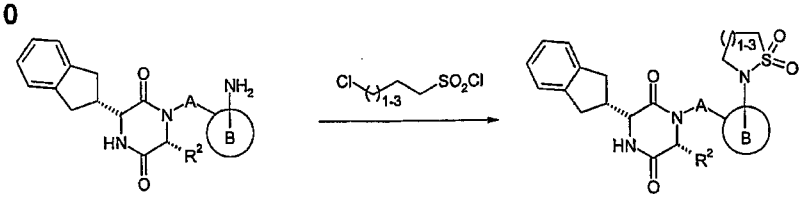
Alternatively, compounds of Formula (I) or Formula (A), wherein R^1 represents the group $-NR^{11}S(O)_mR^{12}$, wherein R^{11} represents an optionally substituted C_{1-4}alkyl group may be prepared according to reaction Scheme 9 by reacting the sulphonamide (Ip) or (Ap) with a suitable alkyl halide $R^{11}Z$, wherein Z is a leaving group such as halogen, for example $R^{11}Z$ is iodomethane, in the presence of a suitable base, such as potassium carbonate in a suitable solvent such as dimethylformamide (DMF).

Scheme 9



Compounds of Formula (I) or Formula (A), wherein R^1 represents the group $-NR^{11}S(O)_mR^{12}$ which forms a cyclised sulphonamide may be prepared according to reaction Scheme 10 starting from the corresponding amine compound (Io) or (Ao) and reacting this with the appropriate chloroalkyl sulfonyl chloride in the presence of a suitable catalyst such as tetrabutyl ammonium iodide.

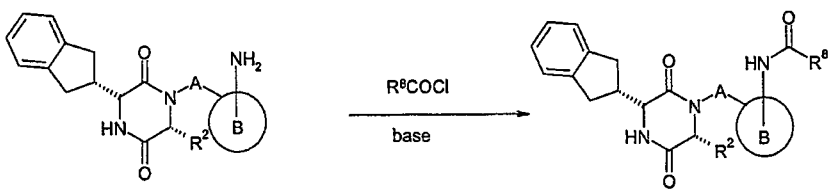
Scheme 10



(Io) or (Ao) (I) or (A)

Compounds of Formula (I) or Formula (A), wherein R^1 represents the group $-NR^7COR^8$ may be prepared according to reaction Scheme 11 by treating the primary amine compound of Formula (Io) or (Ao) with a suitable acid chloride, such as acetyl chloride, in the presence of a suitable solvent, such as dichloromethane, and a base, for example pyridine.

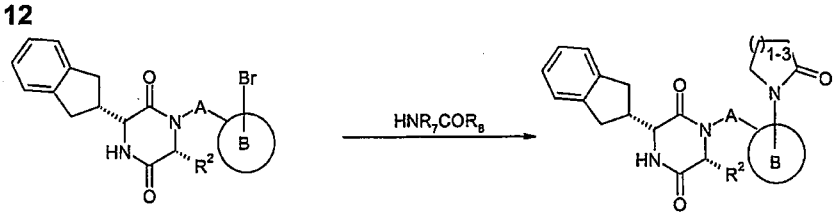
Scheme 11



(Io) or (Ao) (I) or (A)

Compounds of Formula (I) or Formula (A), wherein R^1 represents the group $-NR^7COR^8$, wherein R^7 and R^8 together with the carbonyl group to which they are attached form a cyclic group, may be prepared according to reaction Scheme 12 reacting the bromo compound (Iq) or (Aq) with a suitable amide, HNR^7COR^8, wherein R^7 and R^8 together with the carbonyl group to which they are attached form a cyclic group, in the presence of a suitable catalyst such as copper iodide in a suitable solvent, such as 1,4-dioxan and the mixture subjected to microwave irradiation to form the resulting cyclic amide.

Scheme 12



(Iq) or (Aq) (I) or (A)

Those skilled in the art will appreciate that where a compound of Formula (I) or (A) possesses an amide group anywhere in the molecule, for example the group $-CONR^3R^4$ at the R^1 position, this group may be synthesised for example from a coupling reaction between the corresponding carboxylic acid $-CO_2H$ and an amine HNR^3R^4, using a variety of standard methods. The carboxylic acid may be synthesized by oxidation of the

corresponding aldehyde -CHO or the corresponding alcohol -CH_2OH, or by hydrolysis of the corresponding ester -CO_2R^X, wherein R^X is for example a C_{1-4}alkyl group, or from the corresponding halo compound, for example by treatment with a Grignard reagent in the presence of carbon dioxide.

Those skilled in the art will appreciate that where a compound of Formula (I) or (A) possesses a sulfonamide anywhere in the molecule, for example the group -$SO_2NR^9R^{10}$, this group may be synthesised for example from a reaction between the corresponding sulfonyl chloride -SO_2Cl and an amine, using a variety of standard methods. The sulfonyl chloride -SO_2Cl may be synthesised by oxidation of the corresponding thiol compound -SH using standard conditions, e.g. reaction with sulfuryl chloride in the presence of a suitable base. The thiol compound -SH is accessible from the corresponding sulfanyl compounds -SC_{1-4}alkyl by carrying out a deprotection reaction under standard conditions.

Those skilled in the art will further appreciate that where a compound of Formula (I) or (A) possesses a sulfoxide or sulfone anywhere in the molecule, for example the group -$S(O)_{1-2}R^6$, this group may be may be synthesised for example by an oxidation reaction of the corresponding sulfanyl compound -SR^6 under standard conditions. For example, oxidation of the sulfanyl compound -SR^6 to provide the sulfone compound -SO_2R^6 may be carried out using using a suitable oxidising agent such as 3-chloroperoxybenzoic acid. The sulfanyl compound -SR^6 is accessible by alkylation of the corresponding thiol compound -SH with an alkylating agent R^6X, wherein X is a suitable leaving group, for example mesylate, tosylate or halo, under standard conditions.

Those skilled in the art will also appreciate that in the preparation of the compound of Formula I or a solvate thereof, it may be necessary and/or desirable to protect one or more sensitive groups in the molecule or the appropriate intermediate to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl or aralkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl). Examples of suitable oxygen protecting groups may include for example alky silyl groups, such as trimethylsilyl or *tert*-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or *tert*-butyl; or esters such as acetate.

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Examples

The following examples illustrate the invention. These examples are not intended to limit the scope of the invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the invention. While particular embodiments of the invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

General purification and analytical methods

Analytical HPLC was conducted by one of the following methods:

A) 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 and 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.

B) On an Acquity Ultra Performance LC equipped with a Acquity UPLC BEH C18 1.7 µm column (50 x 2.1 mm, i.d.), eluting with 0.05% TFA in water (solvent A) and 0.05% TFA in acetonitrile (solvent B), using the following elution gradient 5% – 95% (solvent B) over 0.65 minutes and holding at 95% for 0.35 minutes at a flow rate of 0.8 ml/minute.

C) On a Shimadzu LC-2010 HPLC equipped with a YMC-AQ (50 x 2.0 mm ZD) column, eluting with 0.1% TFA in water (solvent A) and 0.05% TFA in acetonitrile (solvent B), using the following elution gradient 10% – 80% (solvent B) over 3.0 minutes and holding at 80% for 0.5 minutes at a flow rate of 0.8 ml/minute.

D) On an Agilent Zorbax SB-C_{18} 5.0 µm column (2.1 mm x 50 mm, i.d.), eluting with 0.05% TFA in water (solvent A) and 0.05% TFA in acetonitrile (solvent B), using the following elution gradient 10% – 99% (solvent B) over 3.0 minutes and holding at 99% for 1.0 minutes at a flow rate of 1.0 mL $minutes^{-1}$.

The mass spectra (MS) were recorded on a Fisons VG Platform or Waters micromass ZQ spectrometer or Finnigan LCQ-Advantage 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 or Avance 300MHz or Avance 400MHz spectrometer using tetramethylsilane as the external standard.

Silica column chromatography refers to purification carried out using prepackaged silica normal phase (RediSep®) cartridges sold by Isco or SPE (solid phase extraction) cartridges sold by International Sorbent Technology Ltd. Aminopropyl SPE and SCX-SPE refer to the aminopropyl and flash SCX-2 cartridges sold by International Sorbent Technology Ltd. Gilson purification refers to purification carried out by high performance liquid chromatography on a Xterra® Prep RP18 5 µm column (30 mm x 100 mm i.d.)

eluting with 0.1% TFA in water and 0.1% TFA in acetonitrile utilizing gradient elution at a flow rate of 25 ml/minute.

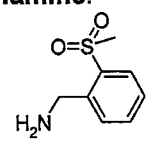
Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cmx10mm i.d.) with 0.1% HCO_2H in water and 95% MeCN, 5% water (0.5% HCO_2H) utilising gradient elution at a flow rate of 8ml minutes^{-1}. The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

Hydrophobic frits refer to filtration tubes sold by Whatman.

Preparative layer chromatography refers to the use of TLC plates sold by Merck coated with silica gel 60 F_{254}.

Intermediate 1

1-[2-(Methylsulfonyl)phenyl]methanamine.



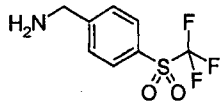
To a vigorously stirred solution of 1-[2-(methylthio)phenyl]methanamine (5g) in dichloromethane (250ml) at 5°C was added the *m*-chloroperoxybenzoic acid (22.7g) portionwise. The reaction was stirred at 0°C for 30 minutes then at 20°C for 18 hours. The reaction was loaded on to 3 x 20g SCX -SPE cartridges, washed with methanol and eluted in 2M ammonia/methanol. Concentration of the latter gave the product as a yellow oil (3.9g, 64%).

LCMS (A) Rt = 0.38 minutes; m/z $[M+H]^+$ = 186

^1H NMR ($CDCl_3$) δ 8.13 (d, 1H), 7.65 (t, 1H), 7.54 (d, 1H), 7.44 (t, 1H), 4.27 (s, 2H), 3.22 (s, 3H), 1.68 (br s, 2.5H (includes water)).

Intermediate 2

1-{4-[(Trifluoromethyl)sulfonyl]phenyl}methanamine.



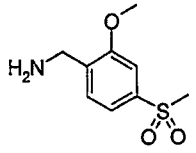
To 4-[(trifluoromethyl)sulfonyl]benzonitrile (1.6g) in THF (20mL) at 20°C was added borane-tetrahydrofuran complex (1.0M, 13.4mL) *via* a cannula. The mixture was stirred for 1 hour before warming to reflux for 18 hours, cooled to 0°C then quenched with methanol (5mL). The mixture was heated to 70°C, and then cooled and the solvent removed *in vacuo*. The resulting residue was dissolved in methanol and passed through a 20g SCX-SPE cartridge. The cartridge was washed with methanol and the product amine eluted with 2.0M ammonia/methanol. Removal of solvent *in vacuo* afforded the amine as a yellow oil (1.4g, 89%).

LCMS (A) Rt = 1.66 minutes; m/z $[M+H]^+$ = 240

^1H NMR ($CDCl_3$) δ 7.98 (d, 2H), 7.68 (d, 2H), 4.09 (s, 2H).

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Intermediate 3
{[2-(Methoxy)-4-(methylsulfonyl)phenyl]methyl}amine hydrochloride.



To a solution of 2-(methoxy)-4-(methylthio)benzoic acid (4.0g) in diethyl ether (10mL) at 0°C was added a solution of lithium aluminium hydride in ethyl ether (1.0M, 30mL), The mixture was stirred at 20°C for 3 days and quenched with water (1.2mL), aqueous NaOH (15%, 1.2mL) and water (3.4mL). Sodium sulfate (anhydrous, 2g) was added and the mixture stirred for 5 minutes whereupon the solid was removed by filtration, washed with ether and the filtrate reduced *in vacuo*. A portion of the residue (0.92g) was dissolved in chloroform (10mL) and diisopropylethylamine (1.1mL) and methane sulfonylchloride (0.46mL) added regulating the temperature below 35°C. The mixture was stirred for 48 hours, water (5mL) added, the aqueous layer extracted with chloroform (2x5mL) and the combined organics reduced *in vacuo*. The resulting residue was dissolved in dimethylformamide (3mL) and added to a mixture of bis(1,1-dimethylethyl) imidodicarbonate (1.3g) and potassium *tert*-butoxide (0.67g) in dimethylformamide (12mL). The mixture was heated to 100°C for 3 hours, cooled to 0°C and quenched with saturated ammonium chloride (15mL). The resulting mixture was reduced by *ca.* 80% *in vacuo* and water (50mL) and ethyl acetate (100mL) added. The supernatant layer was washed with water (2 x 50mL) and saturated brine (50mL) and dried over sodium sulfate before being reduced *in vacuo*. Silica column chromatography (ethyl acetate/cyclohexane) of the residue gave the imido-carbonate (2.2g), 0.49g of which was then dissolved in dichloromethane (7mL) and water (6mL) and sodium hydrogen carbonate (0.49g) and 3-chloroperoxybenzoic acid (1.5g) added. The mixture was stirred for 24 hours and the mixture partitioned between saturated sodium hydrogen carbonate (10mL) and chloroform (10mL). The combined organics were reduced *in vacuo* and the residue purified by silica column chromatography (ethyl acetate/cyclohexane). The resulting sulfone (0.35g) was then dissolved in methanol/dichloromethane (4:1, 10mL) and acetyl chloride (0.35mL) added at 0°C. The mixture was stirred for 24 hours and reduced *in vacuo* to give the title compound (210mg).

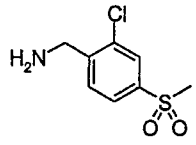
LCMS (A) Rt = 0.38 minutes; m/z $[M+H]^+$ = 216

^{1}H NMR ($CDCl_3$) δ 8.41 (br s, 3H), 7.68 (d, 1H), 7.56 (d, 1H), 7.50 (s, 1H), 4.08 (br q, 2H), 3.95 (s, 3H), 3.31 (s, 3H).

Prior to inclusion in the Ugi reaction the free base of the amine was obtained by means of an aminopropyl-SPE cartridge or by treatment with one equivalent of triethylamine.

Intermediate 4
{[2-Chloro-4-(methylsulfonyl)phenyl]methyl}amine hydrochloride.

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To a solution of 2-chloro-4-(methylsulfonyl)benzoic acid (4.5g) in diethyl ether (10mL) at 0°C was added a solution of lithium aluminium hydride in ethyl ether (1.0M, 30mL), The mixture was stirred at 20°C for 3 days and quenched with water (1.2mL), aqueous NaOH (15%, 1.2mL) and water (3.4mL). Sodium sulfate (anhydrous, 2g) was added and the mixture stirred for 5 minutes whereupon the solid was removed by filtration, washed with ether and the filtrate reduced *in vacuo*. The residue (2.8g) was dissolved in tetrahydrofuran (10mL) and diisopropylethylamine (2.7mL) and methane sulfonylchloride (1.2mL) added regulating the temperature below 35°C. The mixture was stirred for 48 hours, water (5mL) added, the aqueous layer extracted with chloroform (2 x 5mL) and the combined organics reduced *in vacuo*. The resulting residue was dissolved in dimethylformamide (10mL) and added to a mixture of bis(1,1-dimethylethyl) imidodicarbonate (3.4g) and potassium *tert*-butoxide (1.8g) in dimethylformamide (30mL). The mixture was heated to 100°C for 2 hours, cooled to 0°C and quenched with saturated ammonium chloride (30mL). The resulting mixture was reduced by *ca.* 80% *in vacuo* and water (100mL) and ethyl acetate (200mL) added. The supernatant layer was washed with water (2 x 50mL) and saturated brine (50mL) and dried over sodium sulfate before being reduced *in vacuo*. Silica column chromatography (ethyl acetate/cyclohexane) of the residue gave the imido-carbonate (2.3g), which was then dissolved in methanol/dichloromethane (4:1, 10mL) and acetyl chloride (0.35mL) added at 0°C. The mixture was stirred for 24 hours and reduced *in vacuo* to give the title compound (210mg).

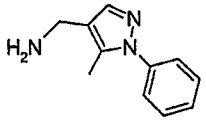
LCMS (A) Rt = 0.3 minutes; m/z $[M+H]^+$ = 220

^{1}H NMR ($CDCl_3$) δ 8.76 (br s., 3H), 8.10 (s, 1H), 7.97 (d, 1H), 7.87 (d, 1H), 4.23 (s, 2H), 3.34 (s, 3H).

Prior to inclusion in the Ugi reaction the free base of the amine was obtained by means of an aminopropyl-SPE cartridge or by treatment with one equivalent of triethylamine.

Intermediate 5

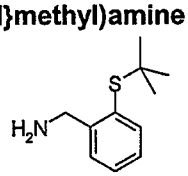
[(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl]amine



A solution of ethyl 5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate (1 g, 4.3 mmol) in dry ether (4 ml) under N_2 was cooled to -75°C. Diisobutyl aluminium hydride (1M in hexane, 8.6 ml) was added over 10 minutes and the reaction stirred at -70°C for 2 hours. Dry methanol (0.85 ml) was then added and the reaction stirred for a further hour. Hydrochloric acid (2M, 4.5 ml) was added and the reaction allowed to warm to room temperature and stirred for 20 minutes. The organic phase was separated and the

aqueous phase extracted with dichloromethane (2 x 50 ml). The combined organics were dried (Na_2SO_4) and concentrated to yield (5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanol as a pale yellow solid (816 mgs, 100%).
LCMS (A) Rt = 2.15 minutes; m/z $[M+H]^+$ = 189
Tetrapropylammonium perruthenate (76 mg) was added to a mixture of (5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanol (816 mg, 4.3 mmol), 4-methylmorpholine N-oxide (754 mg, 6.45 mmol) and molecular sieves (4 Å) in dry dichloromethane (12.6 ml). The reaction was stirred for 40 minutes then filtered through a silica plug washing with dichloromethane. Concentration yielded 5-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde as a pale yellow solid (763 mg, 95 %).
LCMS (A) Rt = 2.39 minutes; m/z $[M+H]^+$ = 187
5-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (763 mg, 4.1 mmol) was dissolved in ethanol (3 ml) and pyridine (3 ml) and hydroxylamine hydrochloride (441 mg, 4.8 mmol) added. The mixture was heated at reflux for 2 hours. The reaction was allowed to cool to room temperature and partitioned between water and chloroform (2 x 20 ml). The organic phase was dried (Na_2SO_4) and concentrated to yield 5-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime as a mixture of isomers, pale yellow solid, (858 mg).
LCMS (A) Rt = 2.38 minutes; m/z $[M+H]^+$ = 202
To a solution of 5-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime (588 mg, 2.93 mmol) in dry tetrahydrofuran (4.8 ml) at 0°C was added lithium aluminium hydride (1 M solution in tetrahydrofuran, 4.4 ml). The reaction was stirred for 1 hour at room temperature and then heated at reflux for 18 hours. The reaction was cooled to 0°C and quenched by the addition of water (0.167 ml), 15% sodium hydroxide (0.167 ml) and water (0.5 ml). Na_2SO_4 (0.33 g) was then added. The reaction was filtered and the filtrate concentrated to give [(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl]amine as a yellow oil (615 mg, 112 % contains some tetrahydrofuran).
LCMS (A) Rt = 1.62 minutes; m/z $[M+H]^+$ = 188
^1H NMR ($CDCl_3$) δ 7.61 (s, 1H) 7.5-7.37 (m, 5H), 3.75 (s, 2H), 2.32 (s, 3H), 1.67 (s, 2H).

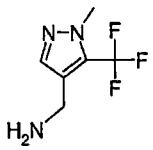
Intermediate 6
({2-[(1,1-Dimethylethyl)thio]phenyl}methyl)amine



Prepared similarly to [(5-methyl-1-phenyl-1H-pyrazol-4-yl)methyl]amine (Intermediate 5) from the commercially available 2-[(1,1-dimethylethyl)thio]benzaldehyde.
^1H NMR (CDCl3) δ 7.55 (dd, 1H), 7.41 (dd, 1H), 7.35 (dt, 1H), 7.23 (dt, 1H), 4.07 (s, 2H), 1.57 (br s, 2H), 1.31 (s, 9H).

Intermediate 7
{[1-Methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}amine

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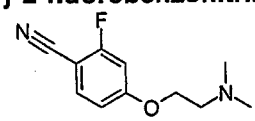
Prepared similarly to [(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl]amine (Intermediate 5) from commercially available ethyl 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate.

LCMS (A) Rt = 0.42 minutes; m/z $[M+H]^+$ = 180

^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H), 3.92 (s, 3H), 3.83 (s, 2H), 1.56 (br s, 2H).

Intermediate 8

4-{[2-(Dimethylamino)ethyl]oxy}-2-fluorobenzonitrile

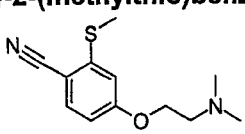


A 1.0M solution of potassium t-butoxide in tetrahydrofuran (7mL) was added slowly to a solution of N,N-dimethylethanolamine (0.75mL, 7.19mmol) in tetrahydrofuran (5mL) at 0-5°C and the solution was stirred for 30 minutes. This mixture was added to a solution of 2,4-difluorobenzonitrile (1.00g, 7.19mmol) in THF (5mL) at -65°C and the resulting mixture was stirred at -65°C for 3 hours, then allowed to warm to room temperature and stirred overnight. The mixture was then cooled to 5°C and quenched with water (40mL) then diluted with diethyl ether (150ml). The organic phase was washed with water (50mL), then with brine (50mL), dried over anhydrous magnesium sulphate and concentrated under reduced pressure to give the title compound as a yellow oil (83%).

^{1}H NMR ($CDCl_3$) δ 7.47 (m, 1H), 6.65 (m, 2H), 4.09 (t, 2H), 2.74 (t, 2H), 2.30 (s, 6H)

Intermediate 9

4-{[2-(Dimethylamino)ethyl]oxy}-2-(methylthio)benzonitrile



Sodium methanethiolate (0.46g) was dissolved in dry THF (30mL); this solution was treated with a solution of 4-{[2-(dimethylamino)ethyl]oxy}-2-fluorobenzonitrile (1.25g) (Intermediate 8) in dry THF (40mL) added over 90 minutes. The mixture was stirred at room temperature overnight. Then was treated with aqueous ammonium chloride (17mL) followed after 10 minutes by aqueous sodium hydrogen carbonate (40mL). The aqueous phase was extracted with dichloromethane (DCM) and the organic phase was washed with aqueous sodium hydrogen carbonate then with brine, dried over anhydrous sodium sulphate then concentrated under reduced pressure to give a ca. 2:1 mixture of 4-{[2-(dimethylamino)ethyl]oxy}-2-fluorobenzonitrile and 4-{[2-(dimethylamino)ethyl]oxy}-2-(methylthio)benzonitrile (1.65g). This was dissolved in dry DMF (5mL) and added to a solution of sodium methanethiolate (0.72g) in dry DMF under nitrogen over 1 hour. This

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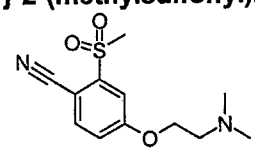
mixture was stirred at room temperature overnight then quenched with aqueous ammonium chloride (30mL) and aqueous sodium hydrogen carbonate (50mL). The aqueous phase was extracted with DCM and the organic phase was washed with aqueous sodium hydrogen carbonate then with brine, dried over anhydrous sodium sulphate then concentrated under reduced pressure to give the title compound as a yellow oil (57%).

LCMS (A) Rt = 1.82 mins, $[M+H]^+$ =237

^{1}H NMR ($CDCl_3$) δ 7.43 (d, 1H), 6.82-6.77 (m, 2H), 4.17 (t, 2H), 2.82 (t, 2H), 2.51 (s, 3H), 2.37 (s, 6H)

Intermediate 10

4-{[2-(Dimethylamino)ethyl]oxy}-2-(methylsulfonyl)benzonitrile

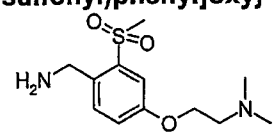


4-{[2-(Dimethylamino)ethyl]oxy}-2-(methylthio)benzonitrile (Int. 9) (1.06g) was dissolved in dry DCM (10mL) under nitrogen and the solution was treated with *m*CPBA (3.35g). The resulting mixture was stirred overnight. DCM (100mL) was added, followed by water (20mL) The aqueous phase was saturated with sodium sulphite and sodium carbonate; the mixture was then stirred for 30 minutes and the phases were separated. The aqueous phase was washed with DCM (x3) and the organic phase was washed with saturated aqueous sodium carbonate. The organic extracts were concentrated under reduced pressure to give the title compound as an oil (47%).

^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1H), 7.56-7.49 (m, 2H), 4.26 (broad s, 2H), 3.05 (s, 3H), 2.83 (broad s, 2H), 2.35 (broad s, 6H)

Intermediate 11

2-{[4-(Aminomethyl)-3-(methylsulfonyl)phenyl]oxy}-*N*,*N*-dimethylethanamine



A solution of 4-{[2-(dimethylamino)ethyl]oxy}-2-(methylsulfonyl)benzonitrile (Int. 10) (0.52g) in glacial acetic acid (40mL) was hydrogenated over 10% palladium on charcoal (0.4g) at 1 atmosphere of hydrogen for 3 hours. After purging the system with nitrogen, the catalyst was removed by filtration under nitrogen and was washed with a small volume of DCM. The combined filtrates were concentrated under reduced pressure to give the crude product as a yellow oil; this was dissolved in 2M hydrochloric acid and the solution was concentrated under reduced pressure, then dissolved in a mixture of methanol and toluene and this solution was concentrated under reduced pressure to afford the dihydrochloride of the title compound. This was converted to the free base using a 10g aminopropyl SPE cartridge eluted with methanol. Product-containing

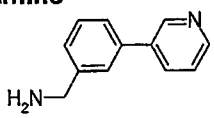
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fractions were combined and evaporated under reduced pressure to give the title compound as a yellow oil (80%).

^{1}H NMR ($CDCl_3$) δ 7.37 (m, 2H), 7.27 (s, 1H), 4.06 (t, 2H), 3.78 (s, 2H), 2.94 (s, 3H), 2.67 (t, 2H), 2.22 (s, 6H)

Intermediate 12

1-[3-(3-Pyridinyl)phenyl]methanamine



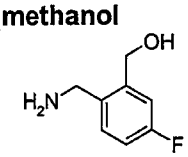
A mixture of 3-bromopyridine (0.12ml, 1.2mmol), [3-(aminomethyl)phenyl]boronic acid (568mg, 3.2mmol) and tetrakis(triphenylphosphine)palladium(0) (39mg, 0.033mmol) in aqueous sodium carbonate (1M, 4ml) and dimethoxyethane (8ml) was heated at reflux for 3 hours and then cooled. The mixture was treated with 50ml of water and extracted with 3x30ml of dichloromethane. The combined organic phase was dried over magnesium sulfate, filtered and evaporated to reveal a yellow oil. The product was purified by chromatography using a 5g bond elute SPE cartridge and eluting with a mixture of dichloromethane, ethanol and aqueous ammonia (200:8:1) to give 100mg (45%) of the title compound as a colourless oil.

LCMS MH+ 185.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.97 (s, 2H), 7.34-7.38 (m, 2H), 7.45–7.48 (m, 2H), 7.54 (bs, 1H), 7.87-7.91 (m, 1H), 8.58-8.61 (m, 1H), 8.84-8.87 (m, 1H).

Intermediate 13

[2-(Aminomethyl)-5-fluorophenyl]methanol



To a solution of 2-bromo-4-fluorobenzonitrile (5g, 25mmol) in anhydrous tertahydrofuran (17 ml) at – 30°C was added isopropylmagnesium chloride (2M in tetrahydrofuran, 15 ml, 30 mmol) and the reaction stirred for 3 hours. Dimethylformamide (5.79 ml, 75 mmol) was then added and the reaction allowed to warm to room temperature and stirred for 1 hour. The reaction was then cooled to – 10°C and hydrochloric acid (2M, 37 ml) added and the reaction stirred for 20 minutes. The reaction was then reduced to ~ 1/3 original volume and partitioned with ethyl acetate. The organics were then dried and concentrated to give 4-fluoro-2-formylbenzonitrile as a brown solid, 2.78 g.

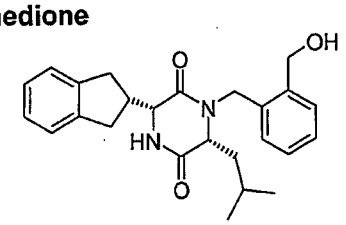
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 10.35 (1H, s); 7.9-7.86 (1H, m); 7.75 (1H, dd, J = 8.16, 2.64 Hz), 7.49-7.44 (1H, m).

LCMS: Ret time 2.25, no ES^+ observed.

To a solution of 4-fluoro-2-formylbenzonitrile (2.78 g, 18.6 mmol) in anhydrous tetrahydrofuran (34 ml) at 0 °C was added lithium aluminiumhydride (1M in tetrahydrofuran, 37.2 ml, 37.2 ml) and the reaction stirred for 1 hour. Water (1.14ml), 15

% sodium hydroxide (1.14 ml) and water (3.42 ml) were sequentially added followed by the addition of sodium sulphate (1.4 g). The reaction was then filtered and concentrated to yield [2-(aminomethyl)-5-fluorophenyl] methanol as a brown oil, 2.8 g.
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.24-7.20 (1H, m); 7.11-7.08 (1H, m); 6.97-6.92 (1H, m); 4.6 (2H, m); 4.0 (2H, m).

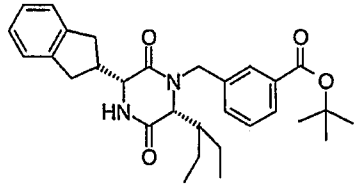
Intermediate 14
(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-{[2-(hydroxymethyl)-phenyl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione



[2-(Aminomethyl)phenyl]methanol (3.509 g, 25.58 mmol) was dissolved in methanol (25ml) and 3-methylbutanal (2.75ml, 25.63 mmol) added followed by (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethanoic acid (7.453 g, 25.58 mmol). The mixture was stirred for 15 minutes before 2-[(phenylmethyl)oxy]phenyl isocyanide (5.35 g, 25.58 mmol) was added. The mixture was stirred for 1.3 hours and then left to stand at room temperature over 7 nights before it was cooled in an ice / water bath. Then acetyl chloride (10.9 ml, 153.4 mmol) was added. Then the mixture was stirred in the cooling bath for a further 10 minutes before it was stirred at room temperature. After 4.25 hours the mixture was evaporated under reduced pressure to leave a dark brown foam. The foam was stirred in chloroform (50 ml) and saturated aqueous sodium bicarbonate solution (40 ml) for 60 minutes before it was diluted with chloroform (100 ml) and the phases separated. The aqueous phase was extracted with chloroform (3 × 50 ml). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to ca. 80 ml. The chloroform solution was treated with glacial acetic acid (2ml) and left to stand, at room temperature for five nights. Then the reaction mixture was washed with 2M hydrochloric acid (70 ml) diluted with chloroform (140 ml) and filtered. The filtered organic phase was washed with saturated aqueous sodium bicarbonate solution (70 ml). The organic phase was dried ($MgSO_4$), evaporated under reduced pressure and dried in vacuo to leave a dark brown solid. The solid was loaded in dichloromethane onto a 330g flash silica chromatography column (pre-eluted with 20% ethyl acetate in cyclohexane). The column was eluted with 20% to 100% ethyl acetate in cyclohexane to afford (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(hydroxymethyl)phenyl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione (1.563 g) as a pale brown foam.
LCMS (A) Rt = 3.17 minutes; m/z $[M+H]^+$ = 407.

Intermediate 15

1,1-Dimethylethyl 3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate

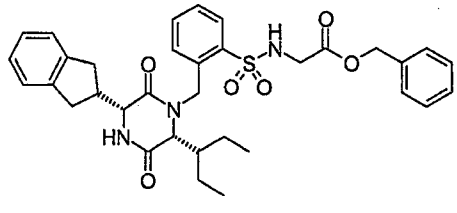


1,1-Dimethylethyl-3-(aminomethyl)benzoate (2.69 g, 12.98 mmol) was dissolved in methanol (15 ml) and 2-ethylbutanal (1.6 ml, 13 mmol) was added followed by (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(phenylmethyl)oxy]carbonyl}amino)ethanoic acid (4.225 g, 12.99 mmol). The mixture was stirred for 11 minutes before 2-[(phenylmethyl)oxy]phenyl isocyanide (2.73 g, 13 mmol) was added. The mixture was stirred at room temperature for 1.8 hours and then left to stand over the weekend (65 hours) before the solvent was evaporated under reduced pressure to leave a sandy foam. The foam in solution in ethanol (90 ml) containing acetic acid (1.5 ml) was hydrogenated at room temperature and pressure over 10 % Pd/carbon (1.42 g) for 18.5 hours. The reaction was filtered through glass fibre filters and the solvent removed *in vacuo* to give a pale brown foam. The foam was stirred in chloroform (50 ml) and treated with glacial acetic acid (2ml). The mixture was stirred overnight (21.5 hours) at room temperature. Then the reaction mixture was diluted with chloroform (100 ml) and washed with 2M hydrochloric acid (40 ml) followed by saturated aqueous sodium bicarbonate solution (40 ml). The phases were separated by hydrophobic frit and the organic phase was evaporated under reduced pressure and dried in vacuo to leave a brown solid. The solid was loaded in dichloromethane onto a 120g flash silica chromatography column (pre-eluted with 10% ethyl acetate in cyclohexane). The column was eluted with 10% to 100% ethyl acetate in cyclohexane to afford 1,1-dimethylethyl 3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate as a pale yellow solid (2.115 g).

LCMS (A) Rt = 3.77 minutes; m/z $[M+H]^+$ = 508.

Intermediate 16

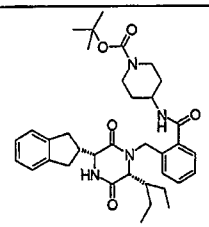
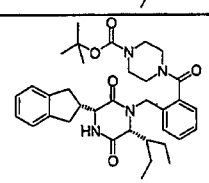
Phenylmethyl N-[(2-{[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo 1-piperazinyl]methyl}phenyl)sulfonyl]glycinate



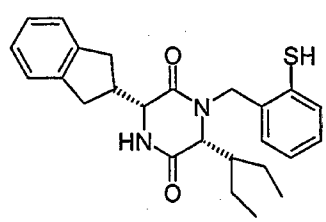
To a solution of 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzenesulfonyl chloride (Int. 20) (100mg) in dichloromethane (2ml) was added diisopropylethylamine (78ul) and phenylmethyl glycinate hydrochloride (39mg) and the mixture stirred for 3 hours at 20°C. Methanol (2ml) was added and the

mixture passed through a 2g aminopropyl-SPE column and the solvent removed. The resulting residue was purified using a 2g Si-SPE column eluting with ethyl acetate/cyclohexate (40-50%) to provide the title compound (69mg) as an oil.
LCMS (A) Rt = 3.67 minutes; m/z $[M+H]^+$ = 618, $[M]^-$ = 616.

Intermediates 17-18 were prepared by methods analogous to that described for Example 66 from 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid (Ex. 65)

Int No	Structure	Mwt	Rt/ min	+ve; -ve	Name
17		616.8	3.48 (A)	617; 615	1,1-dimethylethyl 4-{[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)carbonyl]amino}-1-piperidinecarboxylate
18		602.7	3.62 (A)	603; 601	1,1-dimethylethyl 4-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)carbonyl]-1-piperazine-carboxylate

Intermediate 19
(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-mercaptophenyl)-methyl]-2,5-piperazinedione



To a solution of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(1,1-dimethylethyl)thio]-phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione (Example 60) (8.0g) in acetic acid (80mL) was added 2-nitrobenzenesulfenyl chloride (3.3g) and the mixture stirred at 20°C for 24 hours. The acetic acid was reduced *in vacuo*, the resulting yellow residue dissolved in dimethylformamide (36mL) and the mixture de-gassed by means of a stream of nitrogen gas for 20 minutes. Triethylamine (3.3mL) and tris(carboxyethyl)phosphine hydrochloride (6.7g) were then added and the mixture stirred at 20°C for 1.5 hours under nitrogen. The mixture was reduced *in vacuo* by *ca.* 50% whereupon ethyl acetate (400mL) was added and the mixture washed with de-gassed water (2 x 250mL), brine (200mL) and dried over sodium sulfate. Removal of the

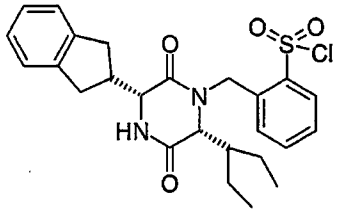
solvent *in vacuo* and silica column chromatography (ethyl acetate/cyclohexane) gave the title compound (5.8g, 82%).

LCMS (A) Rt = 3.7 minutes; m/z $[M+H]^+$ = 423

^{1}H NMR δ 7.15-7.35 (m, 8H), 7.01 (br d, 1H), 5.33 (d, 1H), 4.23 (d, 1H), 4.15 (dd, 1H), 3.52 (br s, 1H), 3.18 (m, 3H), 2.97 (m, 1H), 2.82 (dd, 1H), 1.52- 1.80 (m, 4H), 1.32 (m, 1H), 0.92 (m, 6H).

Intermediate 20

2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzenesulfonyl chloride



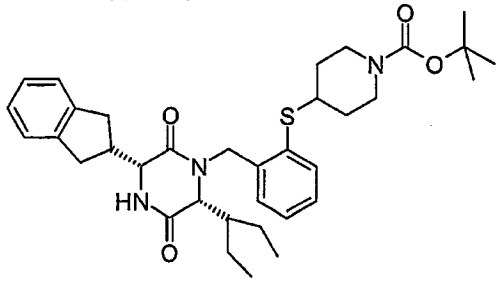
To a solution of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-mercapto-phenyl)methyl]-2,5-piperazinedione (Int. 19) (2.4g) in acetonitrile (60ml) at 0°C was added potassium nitrate (1.7g) followed by dropwise addition of sulfuryl chloride (1.4ml). The mixture was stirred at 0-10°C for 2.5 hours. Sodium carbonate (4g) was dissolved in water (100ml) and added to the reaction at 0°C, the mixture stirred for 2 minutes and partitioned between ethyl acetate (200ml) and water (50ml). The aqueous layer was extracted with ethyl acetate (2 x 50ml) and the combined organics washed with saturated brine (150ml) and dried over sodium sulfate. Removal of the solvent *in vacuo* and silica column chromatography (dichloromethane, chloroform, diethyl ether and ethyl acetate) gave the title compound (1.5g, 54%).

LCMS (A) Rt = 3.7 minutes; m/z $[M+H]^+$ = 489

^{1}H NMR δ 8.14 (d, 1H), 7.70 (t, 1H), 7.55 (t, 1H), 7.31 (d, 1H), 7.2 (m, 5H), 5.43 (d, 1H), 5.04 (d, 1H), 4.20 (dd, 1H), 4.11 (d, 1H), 3.20 (m, 3H), 3.06 (m, 1H), 2.88 (dd, 1H), 1.68 (m, 4H), 1.38 (m, 1H), 0.95 (t, 3H), 0.87 (t, 3H).

Intermediate 21

1,1-Dimethylethyl 4-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)thio]-1-piperidinecarboxylate



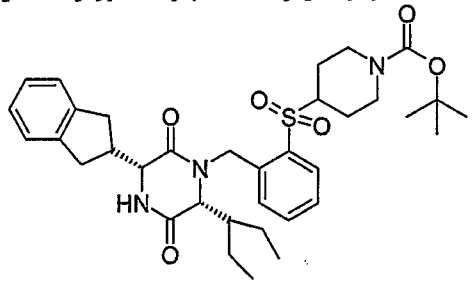
To a solution of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-mercaptophenyl)methyl]-2,5-piperazinedione (Int. 19) (800mg) in acetonitrile (3.2ml) was added 1,1-dimethylethyl 4-[(methylsulfonyl)oxy]-1-piperidinecarboxylate (477mg). The reaction was cooled to 0°C and de-gassed with a stream of nitrogen gas for 20 minutes. Potassium carbonate (330mg) was added and the reaction was heated to 80°C for 3 hours. The reaction was partitioned between water (12ml) and ethyl acetate (12ml) and the aqueous layer extracted with ethyl acetate (2x12ml). The combined organics were concentrated and the residue purified by silica column chromatography (ethyl acetate/cyclohexane) to give the title compound (670mg, 65%).

LCMS (A) Rt = 4.0 minutes; m/z $[M+H]^+$ = 606

^{1}H NMR δ 7.48 (m, 1H), 7.20 (m, 7H), 6.52 (br d, 1H), 5.28 (d,1H), 4.51 (d, 1H), 4.13 (m, 1H), 3.97 (m, 3H), 3.17 (m, 4H), 2.80-3.00 (m, 4H), 1.92 (br d, 2H), 1.62 (m, 5H), 1.48 (s, 9H), 1.29 (m, 1H), 0.88 (m, 1H).

Intermediate 22

1,1-Dimethylethyl 4-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)sulfonyl]-1-piperidinecarboxylate

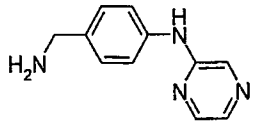


To a solution of 1,1-dimethylethyl 4-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)thio]-1-piperidinecarboxylate (Int. 21) (670mg) in dichloromethane (7.4ml) was added 3-chloroperoxybenzoic acid (570mg) and the mixture stirred for 2 hours. The mixture was quenched by the dropwise addition to 10% sodium sulfite solution (5ml) and the mixture stirred for 5 minutes. The organic layer was separated and the aqueous phase washed with dichloromethane (2 x 5ml) and the combined organics reduced *in vacuo*. The residue was dissolved in methanol and purified by aminopropyl-SPE, eluting the product in methanol. Evaporation in vacuo gave the title compound (690mg, 98%).

LCMS (A) Rt = 3.7 minutes; m/z $[M+H]^+$ = 638

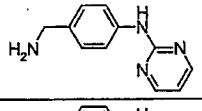
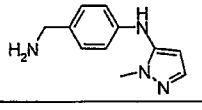
^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H), 7.57 (t, 1H), 7.46 (t, 1H), 7.28 (d, 1H), 7.2 (m, 4H), 6.5 (br d, 1H), 5.32 (d, 1H), 4.80 (d, 1H), 4.25 (br m, 2H), 4.11 (m, 2H), 3.36 (br t, 1H), 3.15 (m, 3H), 2.98 (m, 1H), 2.75 (br m, 3H), 2.08 (br d, 1H), 1.60-1.80 (m, 6H), 1.53 (s, 9H), 1.40 (m, 1H), 1.03 (t, 3H), 0.95 (t, 3H).

Intermediate 23
4-(Pyrazin-2-yl)aminobenzylamine

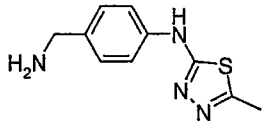


A mixture of 4-bromobenzonitrile (3.76g, 20.8mmol), aminopyrazine (2.4g, 25.3mmol), xantphos (0.26g, 0.45mmol), $Pd_2(dba)_3$ (0.25g, 0.43mmol) and caesium carbonate (9.25g, 28.4mmol) in dioxane (50ml) was heated at reflux under nitrogen for 24 hours. The mixture was cooled, diluted with THF, filtered, concentrated in vacuo then chromatographed (silica, ethyl acetate/petroleum ether 1:3) to give crude 4-(pyrazin-2-yl)aminobenzonitrile (2.64g). Without further purification, this material (2.38g) was hydrogenated in methanolic ammonia (120ml) over Raney nickel (0.36g) at 50 psi for 3 hours. The catalyst was filtered off and the solution evaporated to obtain 4-(pyrazin-2-yl)aminobenzylamine (2.4g).
LCMS (C) Rt = 0.64 minutes; m/z $[M - NH_2]^+$ = 184
^1H NMR ($CDCl_3$) δ 8.21 (d, 1H), 8.10 (m, 1H), 7.96 (d, 1H), 7.38 (d, 2H), 7.30 (d, 2H), 6.65 (br s, 1H), 3.85 (s, 2H).

Intermediates 24-25 were prepared by methods analogous to that described for Intermediate 23

Int. No.	Structure	Mwt	Rt/ min	+ve; -ve	Name
24		200.2	0.61 (C)	184	4-(pyrimid-2-yl)aminobenzylamine
25		202.3	0.53 (C)	203	4-(1-methylimidazol-2-yl)amino-benzylamine

Intermediate 26
4-(5-Methyl-1,4,5-thiadiazol-2-yl)aminobenzylamine



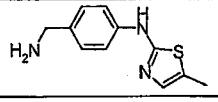
5-Methyl-1,3,4-thiadiazol-2-amine (19 g, 165 mmol) and potassium *tert*-butoxide (24 g, 206 mmol) was dissolved in DMSO (100 mL) and stirred at room temperature for 1 hour. A solution of 4-fluorobenzonitrile (10.8 g, 88.5 mmol) in DMSO (30 mL) was added dropwise over 15 minutes. The reaction was heated to 50 °C and stirred for 30 minutes. The reaction mixture was poured into water (1000 mL) and a precipitate formed. The solution was adjusted to pH = 5 with 2N HCl (100 mL) and then filtered. The precipitate was washed with water and petroleum ether. The solid was dissolved in MeOH and

purified by flash chromatography on silica gel to give 10.2 g of 4-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]benzonitrile. This material (2.2 g, 10.2 mmol) was hydrogenated in methanolic ammonia (125 mL) over Raney nickel (0.40 g, 6.8 mmol) at 50 psi for 3 hours at room temperature. The catalyst was filtered off and the filtrate evaporated to obtain 1.9 g of N-[4-(aminomethyl)phenyl]-5-methyl-1,3,4-thiadiazol-2-amine.

^{1}H NMR (CD_3OD) δ 7.58 (d, 2H), 7.37 (d, 2H), 3.94 (s, 2H), 2.59 (s, 3H)

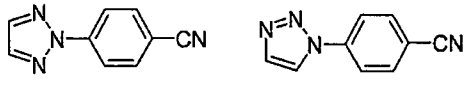
HPLC (C) Rt = 0.80 minutes; m/z $[M+H]^+$ = 221

Intermediate 27 was prepared by methods analogous to that described for Intermediate 23 except sodium carbonate was used as the base.

27		219.3	0.57 (C)	220	4-(5-methylthiazol-2-yl)amino-benzylamine

Intermediates 28 and 29

4-(2*H*-1,2,3-Triazol-2-yl)benzonitrile and 4-(1*H*-1,2,3-triazol-1-yl)benzonitrile



To a solution of 4-bromobenzonitrile (10g, 54.9 mmol) in dry DMF (20ml) was added successively 1*H*-1,2,3-triazole (3.81g, 54.9mmol), copper(I) iodide (0.5g, 2.6mmol), (1*S*,2*S*)-*N*,*N*'-dimethyl-1,2-cyclohexanediamine (1ml, 6.25mmol) and potassium carbonate (16g, 116mmol). The mixture was stirred under nitrogen at 110°C overnight. The solvent was evaporated in vacuo, ethyl acetate was added to the residue and the resulting solution was filtered, dried and evaporated to give a mixture of the two regioisomers. Chromatography gave 4-(2*H*-1,2,3-triazol-2-yl)benzonitrile (Intermediate 28) (3.5g)

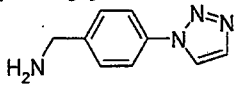
^{1}H NMR ($CDCl_3$) δ 7.79 (2H,d), 7.88 (2H,s), 8.23 (2H,d)

and 4-(1*H*-1,2,3-triazol-1-yl)benzonitrile (Intermediate 29) (2.3g)

^{1}H NMR ($CDCl_3$) δ 7.84-8.07 (6H,m)

Intermediate 30

{[4-(1*H*-1,2,3-Triazol-1-yl)phenyl]methyl}amine



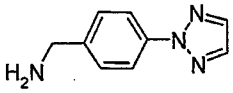
4-(1*H*-1,2,3-Triazol-1-yl)benzonitrile (Intermediate 29) (2.3g, 13.5mmol) in THF (12ml) was cooled in ice and lithium aluminium hydride (2.4g, 63.2mmol) was added portionwise. The mixture was stirred at toom temperature for 1.5h then recooled in ice and aqueous sodium hydroxide (10ml) added dropwise. The resulting solution was filtered, and the THF layer dried and evaporated to obtain {[4-(1*H*-1,2,3-triazol-1-yl)phenyl]methyl}amine (2.5g)

LCMS (C) Rt = 0.45 minutes; m/z $[M+H]^+$ = 175

^{1}H NMR ($CDCl_3$) δ 3.96 (2H,s), 7.49 (2H,d), 7.71 (2H,d), 7.84 (1H,narrow d), 7.98 (1H, narrow d).

Intermediate 31

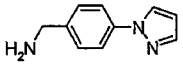
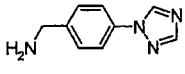
4-(1,2,3-Triazol-2-yl)benzylamine



This compound was prepared from Intermediate 28 by a method analogous to that described for Intermediate 30.

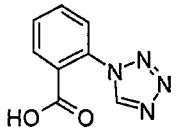
^{1}H NMR ($CDCl_3$) δ 3.92 (2H,s), 7.43 (2H,d), 7.79 (2H,s), 8.03 (2H,d).

Intermediates 32-33 were prepared in two steps by methods analogous to those described for Intermediates 29 and 30 except that in these cases a single regioisomer was obtained

Int. No.	Structure	Mwt	Rt/ min	+ve; -ve	Name
32		173.2	0.66 (C)	157	4-(pyrazol-1-yl)benzylamine
33		174.2	0.44 (C)	158	4-(1,2,4-triazol-1-yl)benzylamine

Intermediate 34

2-(1*H*-Tetrazol-1-yl)benzoic acid

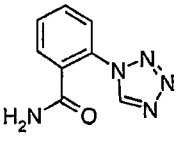


A solution of anthranilic acid (10.0g, 73mmol), sodium azide (14.0g, 217mmol) and trimethyl orthoformate (23.6ml, 220mmol) in glacial acetic acid (250ml) was stirred at room temperature for 2 hours. The resulting solid was filtered off and dried to obtain the desired product (8.73g).

^{1}H NMR ($CDCl_3$) δ 7.46-8.06 (3H,m), 8.26 (1H,m), 9.79 (1H,s)

Intermediate 35

2-(1*H*-Tetrazol-1-yl)benzamide

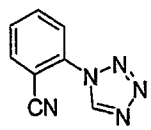


A mixture of 2-(1*H*-tetrazol-1-yl)benzoic acid (Int. 34) (3.0g), ammonium chloride (1.68g), EDC.HCl (6.0g), diisopropylethylamine (10.8ml) and 1-hydroxy-7-azabenzotriazole

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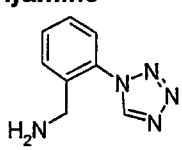
(4.2g) in DMF (45ml) was stirred at room temperature under argon for 15 hours. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried and evaporated to yield the desire product (1.8g).
^{1}H NMR (CD_3OD) δ 7.63-7.79 (4H,m), 9.43 (1H,s)

Intermediate 36
2-(1*H*-Tetrazol-1-yl)benzonitrile



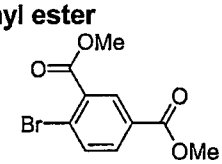
Triethylamine (0.4ml) was added dropwise to a stirred solution of 2-(1*H*-tetrazol-1-yl)-benzamide (Int. 35) (110mg) in phosphorus oxychloride (10ml) at room temperature. After 30 min the mixture was poured into ice-water and extracted with ethyl acetate. Drying and evaporation of the organic layers yielded the desired product (80mg).
^{1}H NMR ($CDCl_3$) δ 7.69-7.94 (4H,m), 9.26 (1H,s)

Intermediate 37
{[2-(1*H*-Tetrazol-1-yl)phenyl]methyl}amine



A solution of 2-(1*H*-tetrazol-1-yl)benzonitrile (Int. 36) (120mg) in methanolic ammonia (20ml) was hydrogenated over Raney nickel (0.5g) at 40 psi for 2 hours. The catalyst was filtered off and the solution evaporated to obtain the desired product (80mg)
LCMS (C) Rt = 0.47 minutes; m/z $[M+H]^+$ = 176

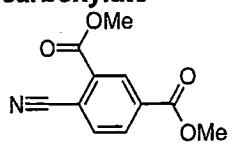
Intermediate 38
4-Bromoisophthalic acid dimethyl ester



A suspension of 4-bromoisophthalic acid (10 g, 40.8 mmol) in MeOH (150 mL) was cooled to 0 °C. Thionyl chloride (10 mL, 140 mmol) was added dropwise over 10 minutes and the reaction stirred at RT overnight. The solvent was then removed. The yellow solid was taken up in 100 mL dichloromethane and washed with 30 mL saturated sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4 and concentrated to yield 4-bromoisophthalic acid dimethyl ester as a white solid (11.0 g, 97%).
LCMS (D) Rt = 2.60 minutes; m/z $[M+H]^+$ = 273

Intermediate 39

Dimethyl 4-cyano-1,3-benzenedicarboxylate



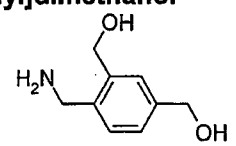
4-Bromoisophthalic acid dimethyl ester (Int. 38) (11 g, 40.3 mmol), copper(I) cyanide (14.4 g, 161.2 mmol), tetraethyl ammonium cyanide (6.38 g, 40.3 mmol), tris(dibenzylideneactone)dipalladium (2.96 g, 3.2 mmol), 1,1'- bis(diphenylphosphino)-ferrocene (7.14 g, 12.9 mmol) and 100 mL dioxane were mixed and refluxed for 2 hours under N_2. The mixture was then cooled down to RT, diluted with 400 mL ethyl acetate and filtered through celite. The filtrate was then washed with 100 mL saturated sodium bicarbonate, dried over $MgSO_4$ and concentrated. The crude material was purified via combi flash silica gel column eluting with 10-50% ethyl acetate in hexanes to give dimethyl 4-cyano-1,3-benzenedicarboxylate as a pale yellow solid (7.1 g, 80%) .

LCMS (D) Rt = 2.23 minutes; m/z $[M+H]^+$ = 220

^1H NMR ($CDCl_3$) δ 8.79 (s, 1H), 8.32 (d, 1H), 7.93 (d, 1H), 4.06 (s, 3H), 4.01 (s, 3H).

Intermediate 40

[4-(Aminomethyl)benzene-1,3-diyl]dimethanol



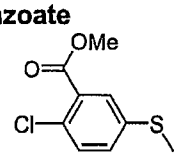
To a suspension of lithium aluminum hydride (2.42 g, 63.9 mmol) in 200 mL dry THF at 0 °C was added dimethyl 4-cyano-1,3-benzenedicarboxylate (Int. 39) (7.0 g, 31.9 mmol) in several batches. The suspension was then warmed up to RT and stirred for 6 hours. After cooling down to 0 °C, 15 mL MeOH was added carefully to quench the reaction, followed by 15 mL water. The resulting mixture was stirred overnight. The suspension was then filtered through 100 g celite and washed with MeOH (5 x 60 mL). The combined filtrate was concentrated and dried in vacuo to give [4-(aminomethyl)benzene-1,3-diyl]dimethanol as a brown oil (5.0 g, 94%).

LCMS (D) Rt = 0.26 minutes; m/z $[M+H]^+$ = 168

^1H NMR (CD_3OD) δ 7.29-7.46 (m, 3H), 4.68 (s, 2H), 4.63 (s, 2H), 3.33 (s, 2H).

Intermediate 41

Methyl 2-chloro-5-(methylthio)benzoate



A solution of 2-chloro-5-(methylthio)benzoic acid (20 g, 94.7 mmol) in MeOH (150 mL) was cooled to 0 °C. Thionyl chloride (10 mL, 140 mmol) was added dropwise over 10 minutes and the reaction stirred at RT overnight. The solvent was then removed. The

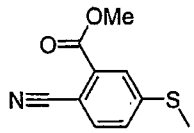
70

yellow solid was taken up in 250 mL ethyl acetate and washed with 30 mL saturated sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4 and concentrated to yield methyl 2-chloro-5-(methylthio)benzoate as a white solid (23.2 g, 100%).

LCMS (D) Rt = 2.76 minutes; m/z $[M+H]^+$ = 217

Intermediate 42

Methyl 2-cyano-5-(methylthio)benzoate

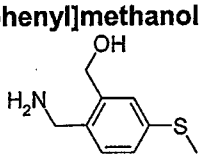


Methyl 2-chloro-5-(methylthio)benzoate (Int. 41) (23.2 g, 106.9 mmol) and copper(I) cyanide (19.2 g, 213.8 mmol) were dissolved in 100 mL N-methylpyrrolidinone. The resulting mixture was heated at 160°C for 72 hours. LCMS showed the presence of the cyanated ester and hydrolyzed acid in 1:1 ratio. After cooling down to RT, the reaction mixture was treated with 250 mL water and 300 mL ethyl acetate and filtered through celite. The phases were separated. The aqueous phase was extracted with 2 x 250 mL ethyl acetate. The combined organics were washed with 250 mL water, dried over $MgSO_4$ and concentrated to give an oil. The crude material was purified via combi flash silica gel column eluting with 0-20% ethyl acetate in hexanes to give methyl 2-cyano-5-(methylthio)benzoate (6.14 g, 28%) as a white solid.

LCMS (D) Rt = 2.42 minutes; m/z $[M+H]^+$ = 208

Intermediate 43

[2-(Aminomethyl)-5-(methylthio)phenyl]methanol



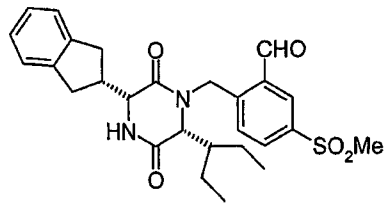
To a suspension of lithium aluminum hydride (3.37 g, 88.9 mmol) in 70 mL dry THF at 0°C was added methyl 2-cyano-5-(methylthio)benzoate (Int. 42) (6.14 g, 29.6 mmol) in several batches. The suspension was then warmed up to RT and stirred for 18 hours. After cooling down to 0 °C, 15 mL MeOH was added carefully to quench the reaction, followed by 15 mL water. The resulting mixture was stirred at RT for 3 hours. The suspension was then filtered through 50 g celite and washed with MeOH (5 x 60 mL). The combined filtrate was concentrated and dried in vacuo to give [2-(aminomethyl)-5-(methylthio)phenyl]methanol (3.80 g, 70%).

LCMS (D) Rt = 0.40 minutes; m/z $[M-NH_3]^+$ = 167

^1H NMR (CD_3OD) δ 7.27 (d, 1H), 7.26 (s, 1H), 4.50 (s, 2H), 3.70 (s, 2H), 3.34 (bs, 1H), 3.17 (s, 3H), 1.92 (bs, 2H).

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Intermediate 44
2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-(methylsulfonyl)benzaldehyde

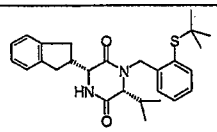


(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione (Ex. 206) (880 mg, 1.76 mmol) was dissolved in dry dichloromethane (5 ml). Dess-Martin Periodinane (1.13 g, 2.64 mmol) was added. The resulting suspension was stirred at RT for 1 hour. The crude reaction mixture was purified directly via combi flash silica gel column eluting with 0-75% ethyl acetate in hexanes to give 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-(methylsulfonyl)benzaldehyde (710 mg, 81%) as a white solid.

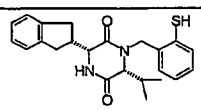
LCMS (D) Rt = 2.73 minutes; m/z $[M+H]^+$ = 497

^{1}H NMR (CD_3OD) δ 10.26 (s, 1H), 8.19 (s, 1H), 7.92 (d, 1H), 7.43 (d, 1H), 7.22 (m, 2H), 7.14 (m, 2H), 5.75 (d, 1H), 5.15 (dd, 1H), 4.75 (dd, 1H), 4.10 (m, 1H), 4.01 (m, 1H), 3.13 (s, 3H), 3.09-3.13 (m, 2H), 2.92 (m, 2H), 1.60-1.75 (m, 4H), 1.35 (m, 1H), 0.96 (t, 3H), 0.93 (t, 3H).

Intermediate 45 was prepared by a method analogous to Example 1, using ({2-[(1,1-dimethylethyl)thio]phenyl}methyl)amine and 2-methylpropionaldehyde.

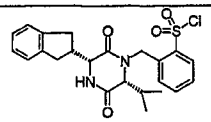
Int. No.	Structure	Mwt	Rt/ min	+ve; -ve	Name
45		450	3.8 (A)	451; -	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-({2-[(1,1-dimethylethyl)-thio]phenyl}methyl)-6-(1-methyl-ethyl)-2,5-piperazinedione

Intermediate 46 was prepared from Intermediate 45 by a method analogous to Intermediate 19

Int. No.	Structure	Mwt	Rt/ min	+ve; -ve	Name
46		394	3.4 (A)	495; -	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(2-mercaptophenyl)methyl]-6-(1-methylethyl)-2,5-piperazinedione

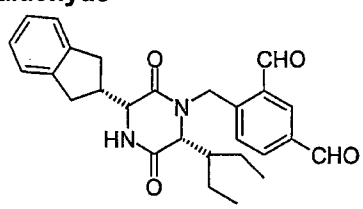
72

Intermediate 47 was prepared from Intermediate 46 by a method analogous to Intermediate 20.

Int. No.	Structure	Mwt	Rt/ min	+ve; -ve	Name
47		460	3.5 (A)	461; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-2,5-dioxo-1-piperazinyl]methyl}benzenesulfonyl chloride

Intermediate 48

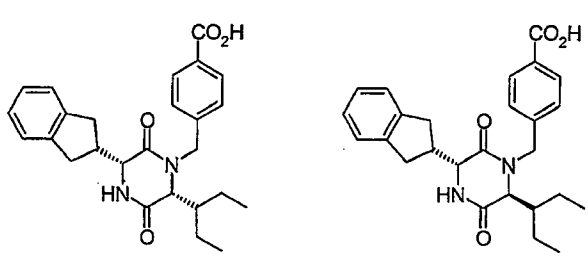
4-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-1,3-benzenedicarbaldehyde



(3*R*,6*R*)-1-{[2,4-Bis(hydroxymethyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (Example 196) (490 mg, 1.1 mmol) was dissolved in dry dichloromethane (5 ml). Dess-Martin Periodinane (1.38 g, 3.3 mmol) was added. The resulting suspension was stirred at RT for 1 hour. The crude reaction mixture was purified directly via combi flash silica gel column eluting with 0-75% ethyl acetate in hexanes to give 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-1,3-benzenedicarbaldehyde (485 mg, 100%) as a white solid.
LCMS (D) Rt = 2.82 minutes; m/z $[M+H]^+$ = 447
^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 10.12 (s, 1H), 8.39 (s, 1H), 8.10 (d, 2H), 7.51 (d, 1H), 7.21-7.28 (m, 3H), 5.43 (d, 1H), 4.98 (d, 1H), 4.11-4.19 (m, 1H), 4.05 (s, 1H), 3.18 (m, 3H), 2.96-3.02 (m, 1H), 2.82-2.88 (m, 1H), 1.50-1.70 (m, 4H), 1.36-.141 (m, 1H), 0.93 (t, 3H), 0.88 (t, 3H).

Intermediate 49

Diastereomeric mixture of 4-{[(3*R*,6*S*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid and 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid



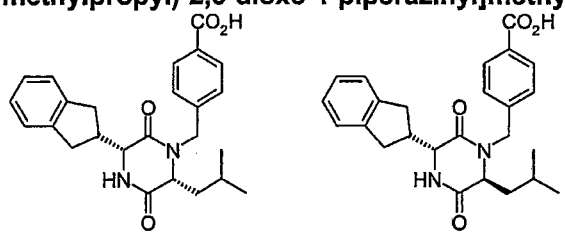
73

To a solution of 1,1-dimethylethyl 4-(aminomethyl)benzoate (0.79 g, 3.81 mmol) in trifluoroethanol (4 mL) was added 2-ethylbutanal (0.47 mL, 3.81 mmol) and stirred at room temperature for 30 minutes. (2R)-2,3-dihydro-1H-inden-2-yl({[(1,1-dimethylethyl)-oxy]carbonyl}amino)ethanoic acid (1.11 g, 3.81 mmol) was added. The reaction mixture was gently heated to dissolve the indanyl glycine. After stirring at room temperature for 30 minutes, 4-chlorophenylisonitrile (0.52 g, 3.81 mmol) was added. The reaction was stirred at room temperature overnight (22 hours) and then cooled in an ice / water bath. Acetyl chloride (1.6 mL, 22.86 mmol) was added dropwise over 30 minutes. The ice bath was removed and the reaction stirred at room temperature over the weekend. The reaction was concentrated under reduced pressure to give a brown solid. Methylene chloride (20 mL) and a saturated aqueous sodium bicarbonate solution (20 mL) were added to the crude residue and then stirred for 30 minutes. The phases were separated and the aqueous phase extracted with EtOAc (3x). The combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give 1.0 g of a sticky brown solid. Chloroform (20 mL) was added to the residue and the resulting solution was treated with glacial acetic acid (0.6 mL) and stirred at room temperature overnight (16 hours). The reaction was concentrated to give a brown oil. Ethyl acetate was added to the residue and then extracted with a saturated aqueous $NaHCO_3$ solution (3x). The combined aqueous extracts were acidified with 2N HCl (pH = 2 – 3) and back extracted with ethyl acetate (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated to give 0.42 g of the title compounds as a yellow solid.

HPLC (D) Rt = 2.70 minutes; m/z $[M+H]^+$ = 435.

Intermediate 50

Diastereomeric mixture of 4-{[(3*R*,6*S*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid and 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid

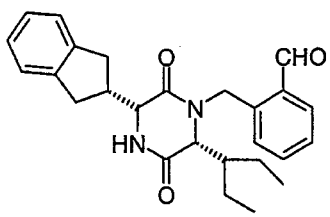


To a solution of 1,1-dimethylethyl 4-(aminomethyl)benzoate (0.70 g, 3.38 mmol) in methanol (4 mL) were added (2R)-2,3-dihydro-1H-inden-2-yl({[(1,1-dimethylethyl)oxy]-carbonyl}amino)ethanoic acid (0.98 g, 3.38 mmol), followed by 4-chlorophenylisonitrile (0.46 g, 3.38 mmol) and then isovaleraldehyde (0.37 mL, 3.38 mmol). The reaction was stirred at room temperature overnight (18 hours) and then concentrated under reduced pressure to give a yellow solid. Methylene chloride (3 mL) was added to the residue and then cooled to 0 °C with an ice bath. 4M HCl dioxane (5 mL, 20.3 mmol) was added dropwise over 30 minutes. The ice bath was removed and the reaction stirred at room

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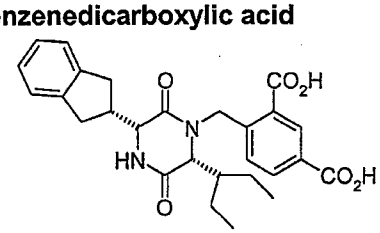
temperature over the weekend. The reaction was concentrated under reduced pressure to give a dark brown oil. Methylene chloride (20 mL) and a saturated aqueous sodium bicarbonate solution (10 mL) were added to the crude residue and then stirred for 30 minutes. The phases were separated. The organic phase was furthered extracted with a saturated aqueous $NaHCO_3$ solution (3x). The combined aqueous extracts were acidified with 2N HCl (pH = 2 – 3) and back extracted with ethyl acetate (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated to give 1.01 g of the title compounds as a yellow solid.
HPLC (D) Rt = 2.61 minutes; m/z $[M+H]^+$ = 421.

Intermediate 51
2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxopiperazin-1-yl]-methyl}benzaldehyde



(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2-(hydroxymethyl)-benzyl]piperazine-2,5-dione (Ex. 1) (4.04g, 9.6 mmol) was dissolved in dry dichloromethane (25 ml) containing 4Å molecular sieves (3.43g). 4-Methylmorpholine N-oxide (1.6g, 13.6 mmol) was added to the stirred mixture followed by tetrapropylammonium perruthenate (101mg, 0.29mmol). The mixture was stirred at room temperature for 90 minutes before it was loaded onto a 40g flash silica chromatography column (pre-eluted with cyclohexane). The column was eluted with 0% to 100% ethyl acetate in cyclohexane to afford 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxopiperazin-1-yl]methyl}benzaldehyde (2.5g) as a pale cream solid.
HPLC (A) Rt = 3.35 minutes; m/z $[M+H]^+$ = 419.
^1H NMR ($CDCl_3$) δ 10.15 (s, 1H), 7.86 (dd, 1H), 7.59 (dt, 1H), 7.52 (br t, 1H), 7.32 (d, 1H), 7.22 (m, 5H), 5.47 (d, 1H), 4.90 (d, 1H), 4.15 (dd, 1H), 4.00 (d, 1H), 3.16 (m, 3H), 2.97 (m, 1H), 2.83 (dd, 1H), 1.63 (m, 4H), 1.34 (m, 1H), 0.88 (m, 6H).

Intermediate 52
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-1,3-benzenedicarboxylic acid



75

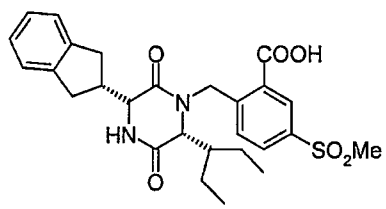
A solution of sulfamic acid (277 mg, 2.86 mmol) in water (2 mL) was added dropwise over 5 minutes to a stirred solution of 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-1,3-benzenedicarbaldehyde (Int. 48) (490 mg, 1.10 mmol) in acetonitrile (20 mL), followed by the dropwise addition of a solution of sodium chlorite (298 mg, 3.30 mmol) in water (3 mL). After the mixture had been stirred at room temperature for 90 minutes it was evaporated under reduced pressure to remove the organic solvent. The aqueous residue was diluted with 5 mL water and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with saturated aqueous sodium chloride solution (10 mL), dried over $MgSO_4$, evaporated under reduced pressure and dried *in vacuo* to afford 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-1,3-benzenedicarboxylic acid as a white solid (490 mg, 98%).

LCMS (D) Rt = 2.47 minutes; m/z $[M+H]^+$ = 479

^{1}H NMR (DMSO) δ 8.54 (s, 1H), 8.43 (s, 1H), 8.09 (d, 1H), 7.35 (d, 1H), 7.22 (s, 2H), 7.12 (s, 2H), 5.10 (d, 1H), 4.87 (d, 1H), 4.00-4.05 (m, 1H), 3.90 (s, 1H), 3.10-3.50 (bs, 1H), 2.80-3.10 (m, 5H), 1.30-1.60 (m, 4H), 1.10-.125 (m, 1H), 0.80 (t, 3H), 0.70 (t, 3H).

Intermediate 53

2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-5-(methylsulfonyl)benzoic acid

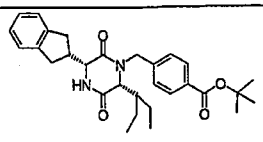


A solution of sulfamic acid (130 mg, 1.30 mmol) in water (2 mL) was added dropwise over 5 minutes to a stirred solution of 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-(methylsulfonyl)benzaldehyde (Int. 44) (500 mg, 1.00 mmol) in acetonitrile (15 mL), followed by the dropwise addition of a solution of sodium chlorite (136 mg, 1.50 mmol) in water (2 mL). After the mixture had been stirred at room temperature for 90 minutes it was evaporated under reduced pressure to remove the organic solvent. The aqueous residue was diluted with 10 mL water and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, evaporated under reduced pressure and dried *in vacuo* to afford 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-(methylsulfonyl)benzoic acid as a white solid (520 mg, 99%).

LCMS (D) Rt = 2.54 minutes; m/z $[M+H]^+$ = 513

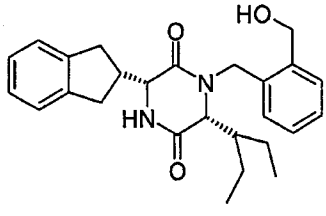
The following intermediate was prepared by a method analogous to Intermediate 15

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Int. No.	Structure	Mwt	Rt/ min	+ve ; -ve	Name
54		490.6	3.79 (A)	491	1,1-dimethylethyl 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate

Example 1

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2(hydroxymethyl)-benzyl]piperazine-2,5-dione



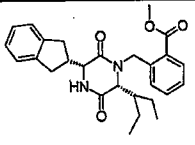
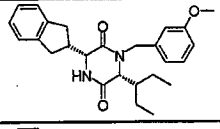
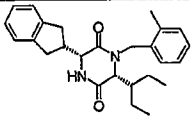
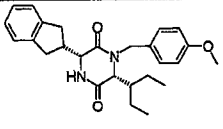
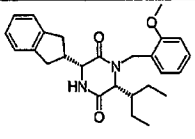
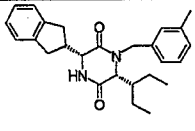
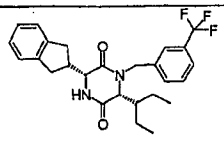
[2-(Aminomethyl)phenyl]methanol (4.12g, 30 mmol) was dissolved in methanol (30ml) and 2-ethylbutanal (3.7ml, 30 mmol) added followed by (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethanoic acid (8.74g, 30 mmol). The mixture was stirred for 15 minutes before 4-chlorophenylisonitrile (4.13g, 30 mmol) was added. The mixture was stirred for 2.25 hours and then left to stand at room temperature overnight (16.3 hours) before it was cooled in an ice / water bath. Then acetyl chloride (12.75ml, 179.5 mmol) was added dropwise, keeping the reaction temperature below 20°C. Then the mixture was stirred in the cooling bath for a further 10 minutes before it was stirred at room temperature. After 5 hours the mixture was evaporated under reduced pressure to leave a dark brown gum. The gum was stirred in chloroform (75ml) and saturated aqueous sodium bicarbonate solution (75ml) for 20 minutes before it was diluted with chloroform (75ml) and the phases separated. The aqueous phase was extracted with chloroform (3 × 75ml). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to ca. 75ml. The chloroform solution was treated with glacial acetic acid (3ml) and left to stand, at room temperature over the weekend. Then the reaction mixture was washed with 2M hydrochloric acid (75ml), followed by saturated aqueous sodium bicarbonate solution (75ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure and dried to leave a brown foam. The foam was loaded in dichloromethane onto a 330g flash silica chromatography column (pre-eluted with 20% ethyl acetate in cyclohexane). The column was eluted with 20% to 100% ethyl acetate in cyclohexane to afford (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2-(hydroxymethyl)benzyl]piperazine-2,5-dione (4.12g) as a pale brown solid.

HPLC (A) Rt = 3.26 minutes; m/z $[M+H]^+$ = 421.

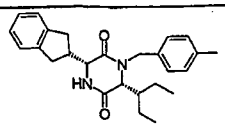
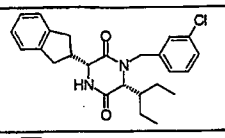
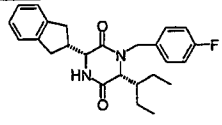
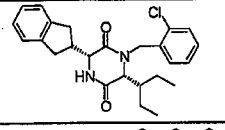
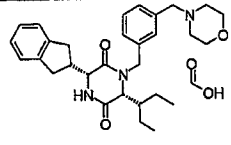
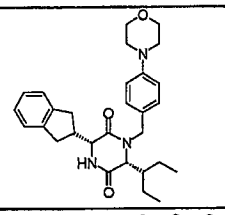
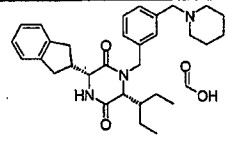
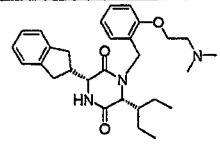
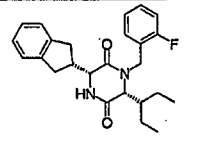
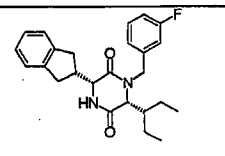
77

^{1}H NMR ($CDCl_3$) δ 7.37 (m, 1H), 7.30 (m, 2H), 7.21 (m, 5H), 6.84 (br d,1H), 5.45 (d, 1H), 4.74 and 4.63 (d, 2H), 4.16 (d, 1H), 4.08 (dd, 1H), 4.04 (d, 1H), 3.15 (m, 3H), 2.92 (m, 1H), 2.78 (m, 2H), 1.76 (m, 1H), 1.62 (m, 3H), 1.31 (m, 1H), 0.92 (m, 6H).

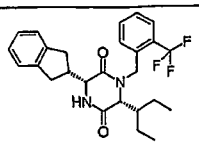
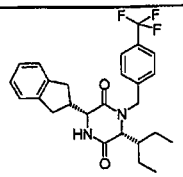
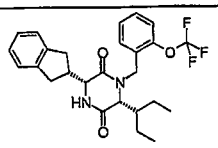
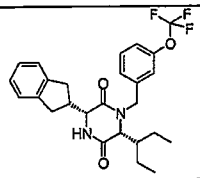
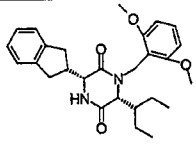
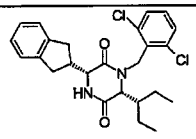
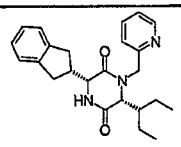
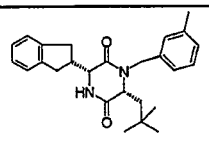
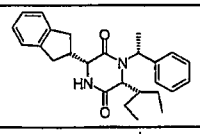
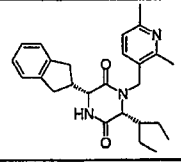
Examples 2-12, 17-31, 33, 43-47 were prepared by methods analogous to that described for Example 1 using 4-chlorophenylisonitrile, optionally with the addition of a base such as triethylamine or DIPEA if the hydrochloride salts of amines were used. In a modification of this method, **Examples 13-16, 32, 34-42, 48** were prepared in a manner analogous to Example 124, using 2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-phenyl isocyanide, optionally with the addition of a base such as triethylamine or DIPEA if the hydrochloride salts of amines were used.

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
2		448.5	3.47 (A)	449; 447	methyl 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-benzoate
3		420.6	3.50 (A)	421; 419	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-methoxy-phenyl]methyl}-2,5-piperazinedione
4		404.6	3.59 (A)	405; 403	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-methylphenyl)methyl]-2,5-piperazinedione
5		420.6	3.48 (A)	421; 419	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-methoxy-phenyl]methyl}-2,5-piperazinedione
6		420.6	3.54 (A)	421; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methoxy)phenyl]methyl}-2,5-piperazinedione
7		404.6	3.60 (A)	405; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione
8		458.5	3.63 (A)	459; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(trifluoromethyl)phenyl]methyl}-2,5-piperazinedione

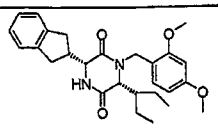
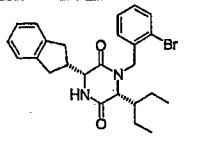
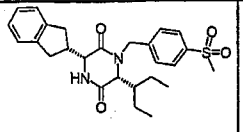
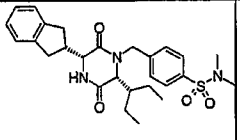
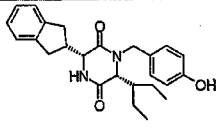
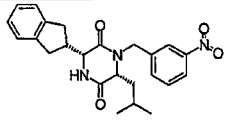
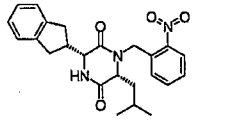
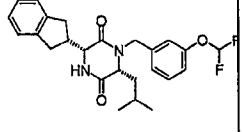
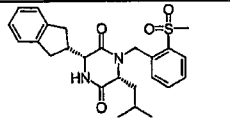
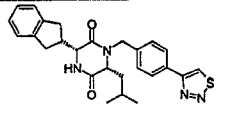
78

9		404.6	3.62 (A)	405; 403	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-methylphenyl)methyl]-2,5-piperazinedione
10		425.0	3.65 (A)	425; 423	(3*R*,6*R*)-1-[(3-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
11		408.5	3.51 (A)	409; 407	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-fluorophenyl)methyl]-2,5-piperazinedione
12		425.0	3.66 (A)	425; 423	(3*R*,6*R*)-1-[(2-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
13		535.7	2.58 (A)	490; 488	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione formate
14		475.6	3.38 (A)	476; 474	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinyl)phenyl]methyl}-2,5-piperazinedione
15		533.7	2.65 (A)	488; 486	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(1-piperidinylmethyl)-phenyl]methyl}-2,5-piperazinedione formate
16		477.7	2.67 (A)	478; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[2-(dimethylamino)-ethyl]oxy}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione
17		408.5	3.54 (A)	409; 407	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-fluorophenyl)methyl]-2,5-piperazinedione
18		408.5	3.54 (A)	409; 407	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(3-fluorophenyl)methyl]-2,5-piperazinedione

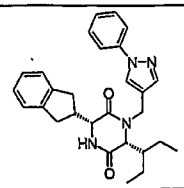
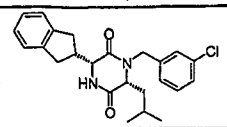
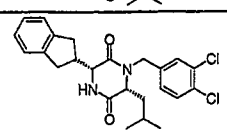
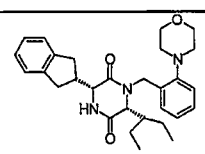
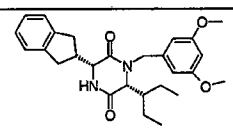
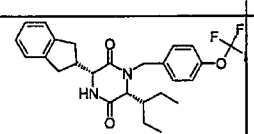
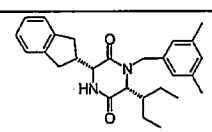
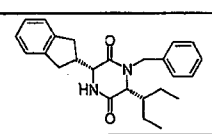
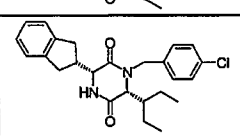
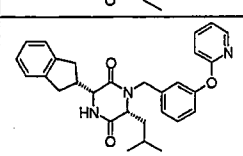
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19		458.5	3.73 (A)	459; 457	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(trifluoromethyl)phenyl]methyl}-2,5-piperazinedione
20		458.5	3.70 (A)	459; 457	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(trifluoromethyl)phenyl]methyl}-2,5-piperazinedione
21		474.5	3.73 (A)	475; 473	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2,5-piperazinedione
22		474.5	3.73 (A)	475; 473	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2,5-piperazinedione
23		450.6	3.50 (A)	451; -	(3*R*,6*R*)-1-{[2,6-bis(methoxy)-phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
24		459.4	3.74 (A)	459/ 461; 455/ 457	(3*R*,6*R*)-1-[(2,6-dichlorophenyl)-methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
25		391.5	3.09 (A)	392; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-pyridinylmethyl)-2,5-piperazinedione
26		404.6	3.69 (A)	405; 403	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2,2-dimethylpropyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione
27		404.6	3.58 (A)	405; 403	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-[(1R)-1-phenylethyl]-2,5-piperazinedione
28		419.6	2.51 (A)	421; 418	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2,6-dimethyl-3-pyridinyl)-methyl]-6-(1-ethylpropyl)-2,5-piperazinedione

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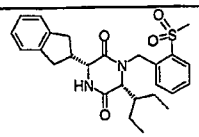
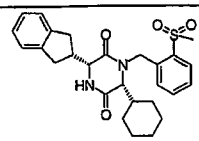
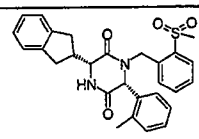
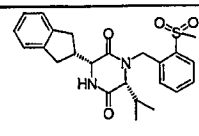
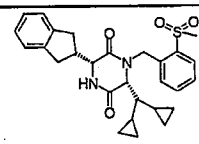
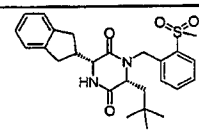
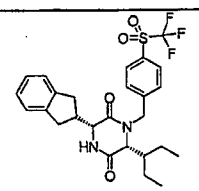
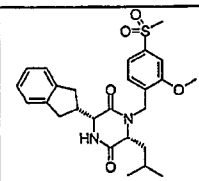
29		450.6	3.53 (A)	451; -	(3*R*,6*R*)-1-{[2,4-bis(methoxy)-phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
30		469.4	3.78 (A)	469/ 471; 467/ 469	(3*R*,6*R*)-1-[(2-bromophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
31		468.6	3.0 (A)	469; 467	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione
32		497.7	3.3 (A)	498; 496	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethyl-benzenesulfonamide
33		406.5	3.29 (A)	407; 405	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-hydroxyphenyl)methyl]-2,5-piperazinedione
34		421.5	3.34 (A)	422; 420	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-[(3-nitrophenyl)methyl]-2,5-piperazinedione
35		421.5	3.35 (A)	422; 420	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-[(2-nitrophenyl)methyl]-2,5-piperazinedione
36		442.5	3.42 (A)	443; 441	(3R,6R)-1-({3-[(difluoromethyl)oxy]phenyl}methyl)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione
37		454.6	3.25 (A)	455; 453	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione
38		460.6	3.49 (A)	461; 459	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2,5-piperazinedione

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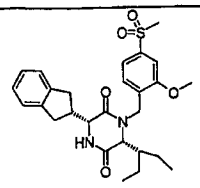
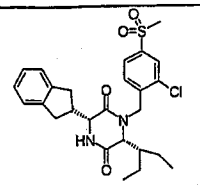
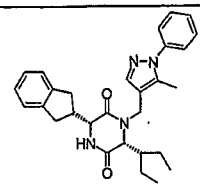
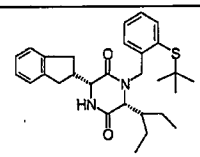
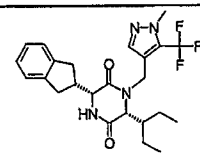
39		456.6	3.55 (A)	457; 455	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-[(1-phenyl-1H-pyrazol-4-yl)methyl]-2,5-piperazinedione
40		410.9	3.52 (A)	411; 409	(3R,6R)-1-[(3-chlorophenyl)methyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione
41		445.4	3.65 (A)	445; 443	(3R,6R)-1-[(3,4-dichlorophenyl)-methyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione
42		475.6	3.47 (A)	476; 474	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinyl)phenyl]methyl}-2,5-piperazinedione
43		450.6	3.48 (A)	451; 449	(3R,6R)-1-{[3,5-bis(methoxy)-phenyl]methyl}-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
44		474.5	3.75 (A)	475; 473	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(trifluoromethyl)oxy]phenyl}methyl)-2,5-piperazinedione
45		418.6	3.74 (A)	419; -	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(3,5-dimethylphenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione
46		390.5	3.51 (A)	391; -	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-(phenyl-methyl)-2,5-piperazinedione
47		425.0	3.66 (A)	425; 423	(3R,6R)-1-[(4-chlorophenyl)methyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
48		469.9	3.37 (A)	470; 468	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-{[3-(2-pyridinyloxy)phenyl]methyl}-2,5-piperazinedione

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Examples 49-61 were prepared by methods analogous to that described for Example 1, using the Intermediates indicated, optionally with the addition of a base such as triethylamine or DIPEA if the hydrochloride salts of amines were used

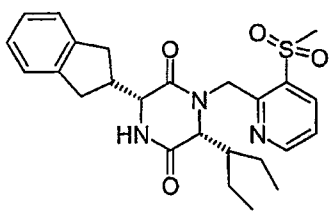
Ex No	Int No	Structure	Mwt	Rt/ min	+ve; -ve	Name
49	1		468.6	3.3 (A)	469; 467	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione
50	1		480.6	3.37 (A)	481; 479	(3*R*,6*R*)-6-cyclohexyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione
51	1		488.6	3.19 (A)	489; 487	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylphenyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione
52	1		376.5	3.36 (A)	377; 375	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione
53	1		492.6	3.55 (A)	429; 427	(3*R*,6*R*)-6-(dicyclopropylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione
54	1		468.6	3.32 (A)	469; 467	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2,2-dimethyl-propyl)-1-{[2-(methylsulfonyl)-phenyl]methyl}-2,5-piperazinedione
55	2		522.3	3.5 (A)	523; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(trifluoromethyl)-sulfonyl]-phenyl}methyl)-2,5-piperazinedione
56	3		484.6	3.3 (A)	485; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-methoxy-4-(methylsulfonyl)phenyl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione

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57	3		498.7	3.2 (A)	499; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-methoxy-4-(methylsulfonyl)-phenyl]methyl}-2,5-piperazinedione
58	4		503.1	3.2 (A)	503; -	(3*R*,6*R*)-1-{[2-chloro-4-(methyl-sulfonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
59	5		470.6	3.31 (A)	471; 515	3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione
60	6		478.7	4.0 (A)	479; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(1,1-dimethyl-ethyl)thio]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione
61	7		462.5	3.47 (A)	463; 461	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione

Example 62

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(methylsulfonyl)-2-pyridinyl]methyl}-2,5-piperazinedione



1-[3-(Methylsulfonyl)-2-pyridinyl]methanamine (186 mg, 1 mmol) and 2-ethylbutanal (124 uL, 1 mmol) were dissolved in chloroform (5 mL) and the mixture was left at room temperature for 63 hours. (2*R*)-2,3-Dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]-carbonyl}amino)ethanoic acid (291 mg, 1 mmol) was added, followed by 4-chlorophenylisonitrile (138 mg, 1 mmol) and the mixture was stirred for 30 minutes at room temperature, then left for 48 hours. The solvent was blown off with nitrogen, the residue taken up in methanol (10 mL) and the solution was cooled to 0°C, then acetyl chloride (0.5 mL) was cautiously added dropwise. The mixture was left at room temperature overnight, then the solvent was blown off with nitrogen and the residue

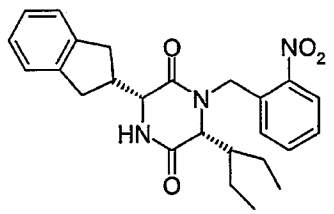
taken up in dichloromethane (10 mL) and stirred with saturated aqueous sodium hydrogen carbonate (5 mL), with solid sodium hydrogen carbonate being added with caution until effervescence ceased. The organic phase was separated using a hydrophobic frit, and treated with glacial acetic acid (0.1 mL). The mixture was left at room temperature overnight. It was then stirred with saturated aqueous sodium hydrogen carbonate (5 mL), with solid sodium hydrogen carbonate being added with caution until effervescence ceased, then the organic phase was separated using a hydrophobic frit. The solvent was removed under reduced pressure and the crude product was purified by mass-directed autoprep followed by preparative layer chromatography on silica (20x20 cm plates, 2 mm thickness) eluted x 3 with 2.5% isopropanol in dichloromethane to give (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(methylsulfonyl)-2-pyridinyl]methyl}-2,5-piperazinedione (33 mg) as an off-white solid.

HPLC (A) Rt = 3.18 mins, $[M+H]^+$ =470

^{1}H NMR ($CDCl_3$) δ 8.72 (dd, 1H), 8.30 (dd, 1H), 7.72 (br d, 1H), 7.42 (dd, 1H), 7.23-7.14 (m, 4H), 5.41 (d, 1H), 5.03 (d, 1H), 4.47 (d, 1H), 4.00 (dd, 1H), 3.42 (s, 3H), 3.18-2.80 (m, 5H), 1.85-1.61 (m, 4H), 1.48-1.35 (m, 1H), 1.04-0.95 (m, 6H)

Example 63

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-nitrobenzyl)piperazine-2,5-dione



[(2-Nitrophenyl)methyl]amine hydrochloride (5.02 g, 26.6 mmol) was dissolved in ethyl acetate (25 ml) and sodium hydrogen carbonate (25 ml) added. The organic phase was separated, dried (Na_2SO_4) and concentrated to give [(2-nitrophenyl)methyl]amine as a yellow oil (2.48 g, 61.4 %).

HPLC Rt = 0.46 minutes; m/z $[M+H]^+$ = 153.

To a solution of [(2-nitrophenyl)methyl]amine (2.48 g, 16.2 mmol) in methanol (50 ml) was added (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]carbonyl}-amino)-ethanoic acid (4.72 g, 16.2 mmol), 2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}phenyl isocyanide (3.78 g, 16.2 mmol) and 2-ethylbutanal (2 ml, 16.2 mmol). The reaction was stirred at room temperature for 18 hours then cooled to 0 °C and acetyl chloride (6.9 ml) added. The reaction was stirred at room temperature for 72 hours. The solvent was removed *in vacuo* and the residue dissolved in chloroform (125 ml). Sodium bicarbonate was added (125 ml) and the biphasic mixture stirred for 3 hours. The organic phase was separated, dried (Na_2SO_4) and concentrated. The residue was dissolved in chloroform (120 ml) and acetic acid (1.2 ml) added and the reaction stirred at room temperature for

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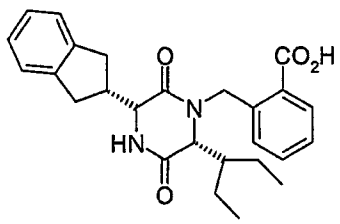
18 hours and then at 50 °C for 1.5 hours. The reaction was then washed with hydrochloric acid (2M, 3 x 100 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated to give a brown solid which was purified by silica column chromatography to give (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-nitrobenzyl) piperazine-2,5-dione as a light brown solid (2.88 g, 44.4 %).

HPLC (A) Rt = 3.39 minutes, m/z $[M+H]^+$ =436

^1H NMR ($CDCl_3$) δ 8.07 (dd, 1H), 7.62 (dt, 1H), 7.48 (dt, 1H), 7.33 (d, 1H), 7.24 (m, 2H), 7.19 (m, 2H), 6.47 (d, 1H), 5.3 (d, 1H), 4.72 (d, 1H), 4.14 (m, 1H), 4.02 (d, 1H), 3.17 (m, 3H), 2.97 (m, 1H), 2.8 (m, 1H), 1.64 (m, 4H), 1.35 (m, 1H), 0.93 (t, 3H), 0.86 (t, 3H).

Example 65

2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid



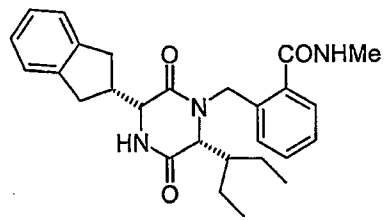
A solution of sulfamic acid (750mg, 7.72mmol) in water (30ml) was added dropwise over 5 minutes to a stirred solution of 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxopiperazin-1-yl]methyl}benzaldehyde (Int. 51) (2.48g, 5.92mmol) in acetonitrile (300ml), followed by the dropwise addition of a solution of sodium chlorite (775mg, 8.57 mmol) in water (30ml). After the mixture had been stirred at room temperature for 70 minutes it was evaporated under reduced pressure to remove the organic solvent. The aqueous residue was partitioned between ethyl acetate (150ml) and water (10ml). The organic phase was washed with saturated aqueous sodium chloride solution (50ml), dried ($MgSO_4$), evaporated under reduced pressure and dried *in vacuo* to afford 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid as a white solid (2.5g).

HPLC (A) Rt = 3.39 minutes; m/z $[M+H]^+$ = 435

^1H NMR ($CDCl_3$) δ 8.27 (d, 1H), 7.98 (d, 1H), 7.53 (dt, 1H), 7.38 (br t, 1H), 7.35 (d, 1H), 7.23 (m, 2H), 7.16 (m,2H), 5.30 (d, 1H), 4.68 (d, 1H), 4.15 (d, 1H), 4.12 (dd, 1H), 3.16 (m, 3H), 2.94 (m, 1H), 2.87 (m, 1H), 1.68 (m, 2H), 1.58 (m, 2H), 1.34 (m, 1H), 0.93 (t, 3H), 0.87 (t, 3H).

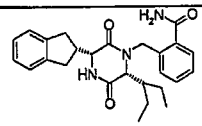
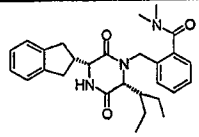
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Example 66
2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide

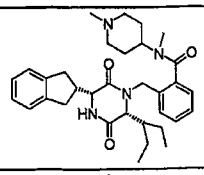
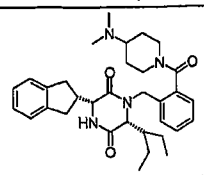
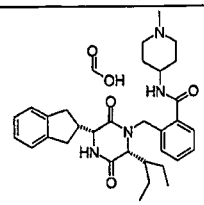
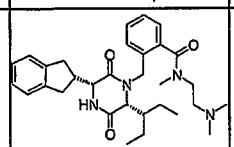
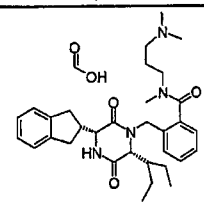
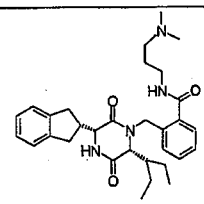
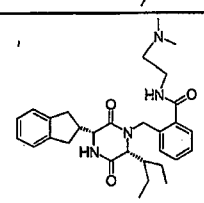
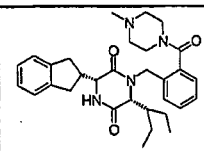
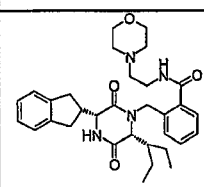


2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid (Ex. 65) (100mg, 0.23 mmol) was dissolved in dry dichloromethane (3ml) and triethylamine (64ul, 0.46 mmol) added, followed after 7 minutes by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (88mg, 0.27 mmol). The mixture was stirred at room temperature for 5 hours before methylamine (0.6ml of a 2M solution in tetrahydrofuran, 1.2 mmol) was added. The mixture was left to stand at room temperature overnight (17 hours) before it was diluted with dichloromethane (2ml) and washed with saturated aqueous sodium bicarbonate solution (2ml). The organic phase was dried (hydrophobic frit) and evaporated to leave a yellow gum. The gum was purified using mass directed autoprep to give 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide as a white solid (73mg).
HPLC (A) Rt = 3.09 minutes; m/z $[M+H]^+$ = 448
^1H NMR ($CDCl_3$) δ 7.54 (br s, 1H), 7.40 (m, 2H), 7.28 (m, 2H), 7.20 (m,4H), 6.60 (br q, 1H), 5.13 (d, 1H), 4.47 (d, 1H), 4.11 (d, 1H), 4.03 (dd, 1H), 3.12 (m, 3H), 3.00 (d, 3H), 2.91 (m, 1H), 2.80 (m, 1H), 1.73 (m, 1H), 1.61 (m, 3H), 1.34 (m, 1H), 0.96 (t, 3H), 0.89 (t, 3H).

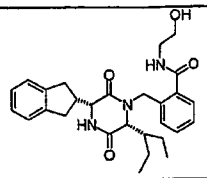
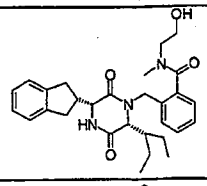
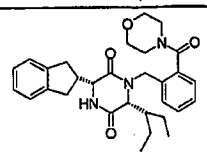
Examples 67-80 were prepared by methods analogous to that described for Example 66 from 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid (Ex. 65)

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
67		433.5	3.05 (A)	434; 432	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzamide
68		461.6	3.2 (A)	462; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*,*N*-dimethylbenzamide

87

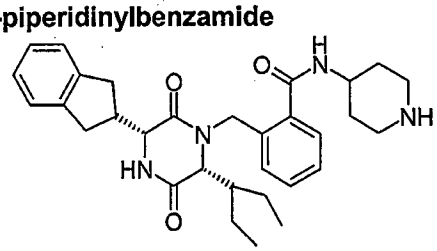
69		544.7	2.63 (A)	545; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-*N*-(1-methyl-4-piperidinyl)benzamide
70		544.7	2.57 (A)	545; 543	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[4-(dimethylamino)-1-piperidinyl]carbonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione
71		576.7	2.52 (A)	531; 529	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(1-methyl-4-piperidinyl)benzamide formate
72		518.7	2.65 (A)	519; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide
73		578.7	2.65 (A)	533; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-[3-(dimethylamino)propyl]-*N*-methylbenzamide formate
74		518.7	2.57 (A)	519; 517	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-[3-(dimethylamino)propyl]benzamide
75		504.6	2.50 (A)	505; 503	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-[2-(dimethylamino)ethyl]benzamide
76		516.6	2.54 (A)	517; 515	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-methyl)-2,5-piperazinedione
77		546.7	2.57 (A)	547; 545	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-[2-(4-morpholinyl)ethyl]benzamide

88

78		477.6	2.91 (A)	478; 476	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)benzamide
79		491.6	3.06 (A)	492; 490	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxy-ethyl)-*N*-methylbenzamide
80		503.6	3.19 (A)	504; 502	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione

Example 83

2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-4-piperidinylbenzamide

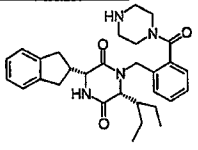


1,1-Dimethylethyl 4-{[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)carbonyl]amino}-1-piperidinecarboxylate (Int. 17) (845mg, 1.37 mmol) was treated with 4M hydrogen chloride in dioxan (3ml, 12 mmol). The mixture was stirred at room temperature for 1 hour before it was evaporated under reduced pressure to leave a yellow foam. The foam was loaded in 1: 1 methanol : dichloromethane onto an SCX-SPE column (pre-eluted with methanol). The column was eluted with methanol, followed by 2M ammonia in methanol. The ammonia in methanol fractions afforded 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-4-piperidinylbenzamide as a pale yellow solid (547mg).

HPLC (A) Rt = 2.54 minutes; m/z $[M+H]^+$ = 517

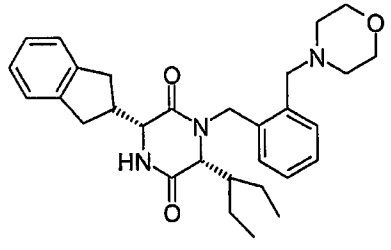
^{1}H NMR ($CDCl_3$) δ 7.44 (br d, 1H), 7.38 (br t, 1H), 7.31 (br t, 1H), 7.24 (m, 2H), 7.18 (m, 4H), 6.78 (m, 1H), 5.12 (d, 1H), 4.45 (d, 1H), 4.13 (d, 1H), 4.07 (m, 1H), 4.03 (dd, 1H), 3.12 (m, 5H), 2.91 (m, 1H), 2.78 (m, 3H), 2.06 (m, 2H), 1.73 (m, 1H), 1.61 (m, 3H), 1.45 (m, 2H), 1.35 (m, 1H), 0.96 (t, 3H), 0.89 (t, 3H).

Example 84 was prepared from Int. 18 by a method analogous to that described for Example 83

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
84		502.6	2.59 (A)	503; 501	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1-piperazinylcarbonyl)phenyl]-methyl}-2,5-piperazinedione

Example 85

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione



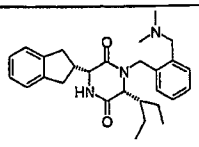
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxopiperazin-1-yl]-methyl}benzaldehyde (Int. 51) (164mg, 0.39 mmol) was dissolved in dry tetrahydrofuran (2.5ml), under nitrogen, and morpholine (34.5ul, 0.39 mmol) added. The stirred mixture was cooled in an ice / water bath and sodium triacetoxyborohydride (118mg, 0.55 mmol) added portionwise. The mixture was stirred for 1.3 hours in the cooling bath before it was stirred at room temperature over 3 days. Then the mixture was partitioned between saturated aqueous ammonium chloride solution (2ml) and dichloromethane (5ml). The organic phase was washed with saturated aqueous sodium bicarbonate solution (2ml), dried (hydrophobic frit) and evaporated to leave a fawn solid. The solid was loaded in dichloromethane onto an SCX-SPE column (5g cartridge, pre-eluted with methanol). The column was eluted with methanol, followed by 2M ammonia in methanol. The ammonia in methanol fractions afforded (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylmethyl)phenyl]methyl}-2,5-piperazinedione as an orange / brown solid (145mg).

HPLC (A) Rt = 2.70 minutes; m/z $[M+H]^+$ = 490

^{1}H NMR ($CDCl_3$) δ 8.65 (br d, 1H), 7.27 (m, 4H), 7.19 (m,4H), 5.41 (d, 1H), 4.47 (d, 1H), 4.15 (dd, 1H), 3.98 (d, 1H), 3.70 (m, 4H), 3.50 (ABq, 2H), 3.21 (m, 2H), 3.14 (m, 1H), 2.97 (m, 1H), 2.89 (m, 1H), 2.44 (m, 4H), 1.69 (m, 4H), 1.35 (m, 1H), 0.92 (t, 3H), 0.90 (t, 3H).

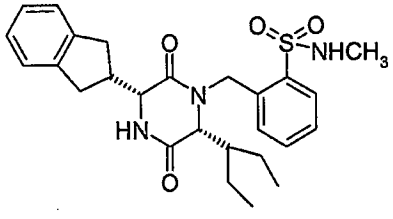
Example 86 was prepared by a method analogous to that described for Example 85.

90

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
86		447.6	2.59 (A)	448; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(dimethylamino)methyl]phenyl}-methyl)-6-(1-ethylpropyl)-2,5-piperazinedione

Example 89

2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzenesulfonamide

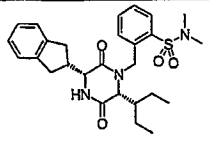
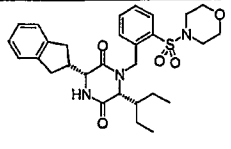


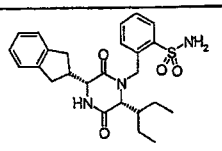
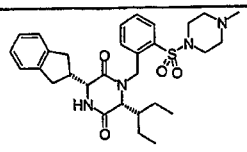
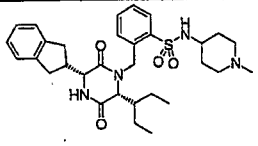
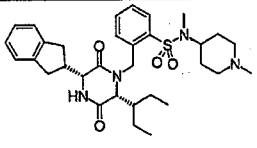
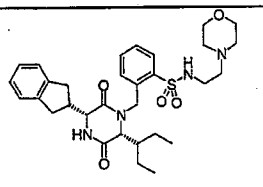
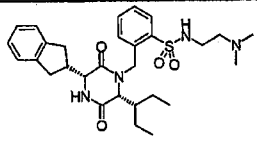
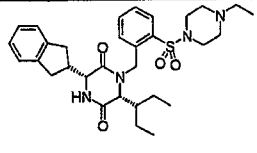
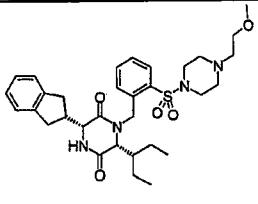
To a solution of 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzenesulfonyl chloride (Int. 20) (100mg) in dichloromethane (2ml) was added diisopropylethylamine (39ul) and methylamine (2M, 0.31ml, 3eq., NB generally 3eq. of volatile amines, 1eq. of non-volatile) and the mixture stirred for 3 hours at 20°C. Methanol (2ml) was added and the mixture passed through a 2g aminopropyl-SPE column to afford the product (85mg, 83%).

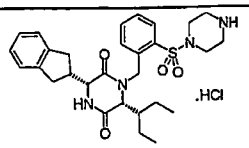
HPLC (A) Rt = 3.4 minutes; m/z $[M+H]^+$ = 484

^{1}H NMR δ 8.03 (d, 1H), 7.54 (t, 1H), 7.45 (t, 1H), 7.32 (d, 1H), 7.22 (m, 4H), 6.47 (br d, 1H), 5.68 (q, 3H), 5.58 (d, 1H), 4.44 (d, 1H), 4.1 (m, 2H), 3.18 (m, 3H), 2.96 (m, 1H), 2.81 (dd, 1H), 2.68 (d, 3H), 1.4-1.8 (m, 5H), 0.96 (2t, 6H).

Examples 90-100 were prepared by methods analogous to that described for Example 89

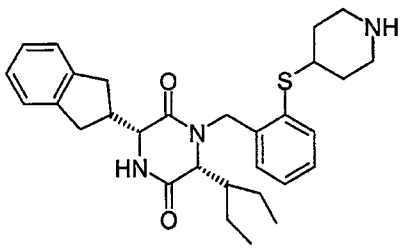
Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
90		497.7	3.4 (A)	498; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethyl-propyl)-2,5-dioxo-1-piper-azinyl]methyl}-*N*,*N*-dimethyl-benzenesulfonamide
91		539.7	3.4 (A)	540; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylsulfonyl)phenyl]-methyl}-2,5-piperazinedione

92		469.6	3.2 (A)	470; 468	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-benzene-sulfonamide
93		552.7	2.6 (A)	553; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methyl-1-piperazinyl)sulfonyl]-phenyl}-methyl)-2,5-piperazine-dione
94		566.8	2.6 (A)	567; 565	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(1-methyl-4-piperidinyl)-benzene-sulfonamide
95		580.8	2.7 (A)	581; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethyl-propyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-*N*-(1-methyl-4-piperidinyl)-benzenesulfonamide
96		582.8	2.7 (A)	583; 581	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-[2-(4-morpholinyl)ethyl]benzene-sulfonamide
97		540.7	2.7 (A)	541; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-[2-(dimethylamino)ethyl]benzene-sulfonamide
98		566.8	2.8 (A)	567; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(4-ethyl-1-piperazinyl)-sulfonyl]phenyl}methyl)-6-(1-ethyl-propyl)-2,5-piperazinedione
99		596.8	2.8 (A)	597; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-({4-[2-(methoxy)ethyl]-1-piperazinyl}-sulfonyl)phenyl]methyl}-2,5-piperazinedione

100		575.2	2.7 (A)	539; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1-piperazinylsulfonyl)phenyl]methyl}-2,5-piperazinedione hydrochloride

Example 102

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylthio)-phenyl]methyl}-2,5-piperazinedione.



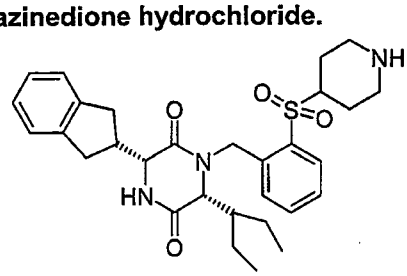
To a solution of 1,1-dimethylethyl 4-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)thio]-1-piperidinecarboxylate (Int. 21) (45mg) in dichloromethane (0.2mL) was added 4M hydrogen chloride in dioxan (0.1mL) and the mixture stirred for 2 hours. The mixture was reduced *in vacuo* and purified by aminopropyl-SPE and mass-directed autoprep to give the title compound (12.2mg).

HPLC (A) Rt = 2.8 minutes; m/z $[M+H]^+$ = 506

^{1}H NMR δ 7.45 (m, 1H), 7.20 (m, 7H), 6.54 (br s, 1H), 5.32 (d, 1H), 4.51 (d, 1H), 4.17 (dd, 1H), 4.02 (d, 1H), 3.20 (m, 5H), 3.00 (m, 1H), 2.84 (dd, 1H), 2.75 (t, 2H), 1.95-2.20 (br m, 5H), 1.70 (m, 5H), 1.32 (m, 1H), 0.92 (m, 6H).

Example 104

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylsulfonyl)-phenyl]methyl}-2,5-piperazinedione hydrochloride.



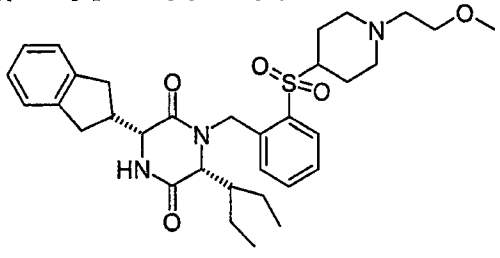
To a solution of 1,1-dimethylethyl 4-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)sulfonyl]-1-piperidinecarboxylate (Int. 22) (94mg) in dichloromethane (0.4mL) was added 4M hydrogen chloride in dioxan (0.27mL) and the mixture stirred for 3 days. The solvent was removed *in vacuo* to give the title compound (80mg).

HPLC (A) Rt = 2.7 minutes; m/z $[M+H]^+$ = 538

^{1}H NMR ($CDCl_3$) δ 8.80 (br s, 2H), 8.53 (br d, 1H), 7.88 (d, 1H), 7.78 (t, 1H), 7.59 (t, 1H), 7.34 (d, 1H), 7.20 (m, 2H), 7.11 (m, 2H), 5.16 (d, 1H), 4.87 (d, 1H), 4.03 (dd, 1H), 3.96 (d, 1H), 3.74 (tt, 1H), 3.34 (m, 2H (obscured by water)), 2.80-3.05 (m, 6H), 2.07 (br d, 1H), 1.90 (m, 3H), 1.45-1.66 (m, 4H), 1.26 (m, 1H), 0.89 (t, 3H), 0.78 (t, 3H).

Example 105

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-({1-[2-methoxy-ethyl]-4-piperidinyl}sulfonyl)phenyl]methyl}-2,5-piperazinedione



A solution of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylsulfonyl)phenyl]methyl}-2,5-piperazinedione hydrochloride (Ex. 104) (150 mg, 0.26 mmol) in methanol was loaded onto an aminopropyl SPE column, washing with methanol. Concentration yielded (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylsulfonyl)phenyl]methyl}-2,5-piperazinedione as a green oil (131 mg, 93%).

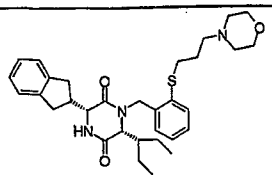
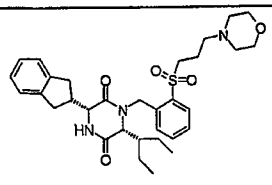
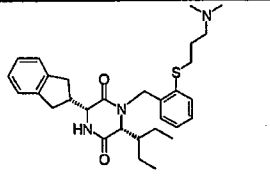
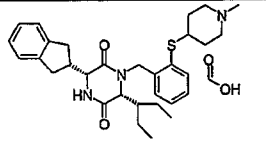
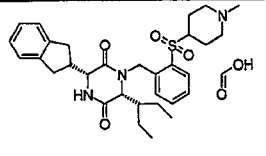
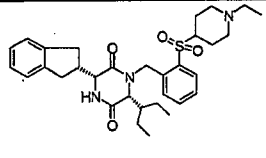
HPLC (A) Rt = 2.66 minutes; m/z $[M+H]^+$ = 538

To a solution of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylsulfonyl)phenyl]methyl}-2,5-piperazinedione (131 mg, 0.24 mmol) in dimethylformamide (0.6 ml) was added potassium carbonate (40 mg, 0.29 mmol), 2-bromoethylmethylether (22.6 µL, 0.24 mmol) and tetrabutylammoniumiodide (18 mg, 0.05 mmol). The reaction was heated to 50°C for 3 hours. Further 2-bromoethylmethylether (22.6 µL, 0.24 mmol), tetrabutylammoniumiodide (18 mg, 0.05 mmol) and potassium carbonate (40 mg, 0.29 mmol) were added and the reaction was heated at 50°C for 1 hour. The reaction was loaded onto an SCX –SPE column, washed with methanol then eluted with 2M ammonia/methanol. Concentration gave (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-({1-[2-(methoxy)ethyl]-4-piperidinyl}sulfonyl)phenyl]methyl}-2,5-piperazinedione as a clear oil (117 mg, 82%).

HPLC (A) Rt = 2.72 minutes; m/z $[M+H]^+$ = 596

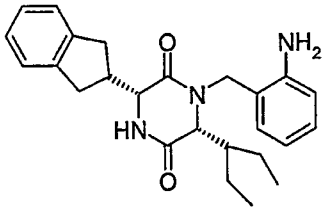
^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1H), 7.6 (t, 1H), 7.5 (t, 1H), 7.35-7.2 (m, 5H), 6.5 (br s, 1H), 5.35 (d, 1H), 4.95 (d, 1H), 4.15 (dd, 1H), 4.05 (d, 1H), 3.5 (m, 2H), 3.35 (s, 3H), 3.2-2.95 (m, 7H), 2.85 (m, 1H), 2.58 (m, 2H), 2.05-1.8 (m, 6H), 1.75-1.5 (m, 4H), 1.33 (m, 1H), 0.95 (t, 3H), 0.85 (t, 3H).

Examples 106-111 were prepared by methods analogous to that described for Intermediate 21 (sulfides) and Intermediate 22 (sulfones).

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
106		549.7	2.79 (A)	550; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-{[3-(4-morpholinyl)-propyl]thio}phenyl)methyl]-2,5-piperazinedione
107		581.7	2.74 (A)	582; 580	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-{[3-(4-morpholinyl)-propyl]sulfonyl}phenyl)methyl]-2,5-piperazinedione
108		507.7	2.71 (A)	508; 506	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]thio}phenyl)methyl]-6-(1-ethyl-propyl)-2,5-piperazinedione
109		565.7	2.81 (A)	520; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methyl-4-piperidinyl)thio]phenyl}-methyl)-2,5-piperazinedione formate
110		597.7	2.71 (A)	552; 549	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methyl-4-piperidinyl)sulfonyl]phenyl}-methyl)-2,5-piperazinedione formate
111		565.8	2.70 (A)	566; 564	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(1-ethyl-4-piperidinyl)sulfonyl]phenyl}-methyl)-6-(1-ethylpropyl)-2,5-piperazinedione

Example 112

(3*R*,6*R*)-1-[(2-Aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione



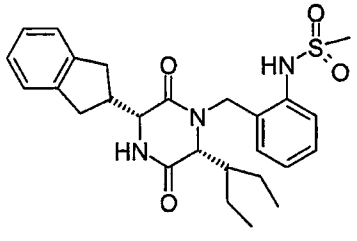
A solution of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-nitrobenzyl)-piperazine-2,5-dione (Ex. 63) (1.99g, 4.57 mmol) in ethanol (36 ml) was hydrogenated at room temperature and pressure over 10 % Pd/carbon (707 mg) for 2.5 hours. The reaction was filtered through celite and the solvent removed *in vacuo* to give (3*R*,6*R*)-1-[(2-aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazine-dione as a light brown solid (1.79 g, 97 %).

HPLC (A) Rt = 3.34 minutes; m/z $[M+H]^+$ = 406/407

^{1}H NMR ($CDCl_3$) δ 7.25 (m, 1H), 7.18 (m, 3H), 7.13 (dt, 1H), 7.05 (dd, 1H), 6.68 (m, 3H), 5.45 (d, 1H), 4.29 (br s, 2H), 4.07 (dd, 1H), 4.03 (d, 1H), 3.91 (d, 1H), 3.14 (m, 3H), 2.93 (m, 1H), 2.76 (m, 1H), 1.88 (m, 1H), 1.67 (m, 2H), 1.25 (m, 2H), 1.00 (t, 3H), 0.94 (t, 3H).

Example 113

***N*-(2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl] methyl}phenyl)methanesulfonamide**



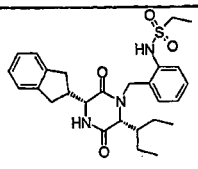
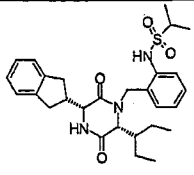
To a solution of (3*R*,6*R*)-1-[(2-aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (Ex. 112) (150 mg, 0.37 mmol) in dry dichloromethane (2.5 ml) at 0 °C was added triethylamine (0.26 ml) and 4-dimethylaminopyridine (450 µg). After five minutes mesyl chloride (34 µl, 0.74 mmol) was added and the reaction stirred at room temperature until absence of starting material was detected by LCMS. The reaction was concentrated and the residue dissolved in tetrahydrofuran (3.5 ml) and treated with 1M sodium hydroxide solution (0.7 ml). After one hour the reaction was neutralised and extracted with ethyl acetate (5 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography to yield *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl] methyl}phenyl)methanesulfonamide as a white solid (111 mg, 62 %).

HPLC (A) Rt = 3.15 minutes; m/z $[M+H]^+$ = 484

^{1}H NMR ($CDCl_3$) δ 9.2 (s, 1H), 7.58 (d, 1H), 7.39 (dt, 1H), 7.25 (m, 1H), 7.23-7.13 (m, 5H), 6.38 (br d, 1H), 5.13 (d, 1H), 4.19 (d, 1H), 4.12 (d, 1H), 4.06 (dd, 1H), 3.18 (m, 3H),

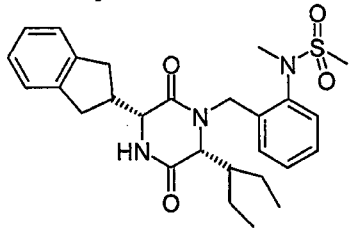
3.1 (s, 3H), 2.90 (m, 1H), 2.7 (m, 1H), 1.84 (m, 1H), 1.70 (m, 2H), 1.65 (m, 1H), 1.32 (m, 1H), 1.09 (t, 3H), 0.94 (t, 3H).

Examples 114-115 were prepared by methods analogous to that described for Example 113

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
114		497.6	3.25 (A)	498; 496	*N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-ethane-sulfonamide
115		511.6	3.5 (A)	512; 510	*N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-2-propanesulfonamide

Example 116

***N*-(2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-*N*-methylmethanesulfonamide**



To a solution of *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)methanesulfonamide (Ex. 113) (178 mg, 0.37 mmol) in dimethylformamide (1 ml) was added potassium carbonate (102 mg, 0.74 mmol) followed by iodomethane (69 µl, 1.1 mmol) and the reaction stirred at room temperature for 18 hours. The reaction was quenched by the addition of ammonia in methanol solution (2M, 0.74 ml). The reaction was then diluted with dichloromethane (4 ml) and water (4 ml). The organic phase was separated, passed through a hydrophobic frit and concentrated. The residue was purified by silica column chromatography to yield *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-*N*-methylmethanesulfonamide as a white solid (62 mg, 34 %).

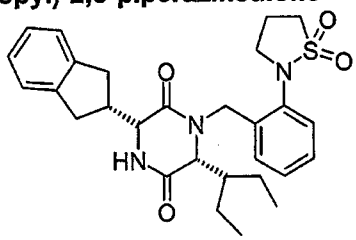
HPLC (A) Rt = 3.32 minutes; m/z $[M+H]^+$ = 498

^{1}H NMR at room temperature showed clear rotomers which coalesced at 120 °C to give the following spectrum: ^{1}H NMR (DMSO-d6, 120 °C): δ 7.91 (br s 1H), 7.50 (m, 1H), 7.36

(m, 2H), 7.23 (m, 3H), 7.15 (m, 2H), 5.06 (d, 1H), 4.43 (d, 1H), 3.98 (dd, 1H), 3.84 (d, 1H), 3.22 (m, 3H), 3.10-2.98 (m, 8H), 1.6-1.28 (m, 5H), 0.92-0.8 (m, 6H).

Example 117

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-{[2-(1,1-dioxido-2-isothiazolidinyl)-phenyl]methyl}-6-(1-ethylpropyl)-2,5-piperazinedione



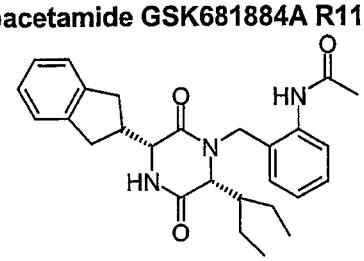
To a solution of (3*R*,6*R*)-1-[(2-aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (Ex. 112) (130 mg, 0.32 mmol) in dichloromethane (1.5 ml) at 0°C was added triethylamine (0.22 ml) followed by 3-chloropropane sulfonyl chloride (77 ul, 0.64 mmol). Tetrabutyl ammonium iodide (1.2 mg) was added and the reaction stirred at room temperature for 18 hours. The reaction was concentrated and the residue dissolved in ethanol (1 ml), treated with triethylamine (0.11 ml) and heated at reflux for 5 hours. The reaction was concentrated and the residue dissolved in dichloromethane and washed with water. The organic phase was collected via a hydrophobic frit, concentrated and the residue purified by silica column chromatography to give (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(1,1-dioxido-2-isothiazolidinyl)-phenyl]methyl}-6-(1-ethylpropyl) -2,5-piperazinedione as a pale yellow solid (58 mg, 36 %).

HPLC (A) Rt = 3.3 minutes; m/z $[M+H]^+$ = 510

^{1}H NMR ($CDCl_3$) δ 7.51 (d, 1H), 7.35 (m, 3H), 7.12 (m, 5H), 5.28 (d, 1H), 4.31 (d, 1H), 4.06 (m, 2H), 3.69 (m, 2H), 3.37 (m, 2H), 3.15 (m, 3H), 2.93 (m, 1H), 2.79 (m, 1H), 2.57 (m, 2H), 1.77 (m, 1H), 1.64 (m, 3H), δ 1.3 (m, 1H), 0.95 (m, 6H).

Example 118

N-(2-{[(3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)acetamide GSK681884A R11351/189/1



To a solution of (3*R*,6*R*)-1-[(2-aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (Ex. 112) (70mg, 0.17mmol) in anhydrous dichloromethane (1ml) under an atmosphere of nitrogen was added pyridine (32ul) and acetyl chloride (14.7ul). After stirring for 16hr the reaction mixture was partitioned

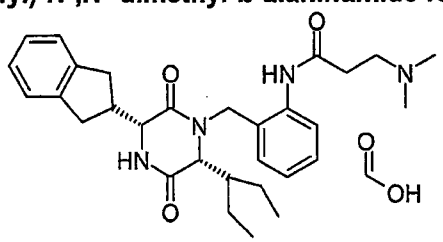
between dichloromethane and water. The phases were separated via a hydrophobic frit and the organic phase was loaded onto a 2g SCX-SPE cartridge and eluted with methanol. Evaporation of the methanol *in vacuo* and freeze drying from dioxan gave N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)acetamide as a white lyophilate (42mg).

HPLC (A) Rt = 3.21 minutes; m/z $[M+H]^+$ = 448

^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1H); 8.28 (d, 1H); 7.37 (t, 1H); 7.27 (t, 1H); 7.20 (m, 4H); 7.07 (t, 1H); 6.85 (s, 1H); 5.25 (d, 1H); 4.16 (d, 1H); 4.04 (m, 1H); 4.01 (d, 1H); 3.15 (m, 3H); 2.91 (m, 1H); 2.78 (m, 1H); 2.26 (s, 3H); 1.88 (m, 1H); 1.70 (m, 2H); 1.56 (m, 1H); 1.31 (m, 1H); 1.1 (t, 3H); 0.96 (t, 3H)

Example 119

***N*^{1}-(2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-*N*^{3},*N*^{3}-dimethyl-ß-alaninamide formate**

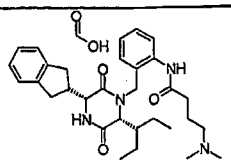
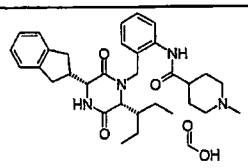


To a solution of (3*R*,6*R*)-1-[(2-aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (Ex. 112) (70mg, 0.17mmol) in anhydrous dichloromethane (1 ml) under an atmosphere of nitrogen was added pyridine (32ul) and *N*,*N*-dimethyl-ß-alanyl chloride hydrochloride (36mg). After stirring for 16hr the reaction mixture was partitioned between dichloromethane and water. The phases were separated via a hydrophobic frit and the organic phase was loaded onto a 2g SCX-SPE cartridge and eluted with methanol, then 1N ammonia in methanol. The basic fraction was evaporated *in vacuo* and the residue further purified using the mass-directed autoprep system. Freeze drying from dioxan gave N^1-(2-{[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-N^3,N^3-dimethyl-ß-alaninamide formate (18.8mg) as a white lyophilate.

HPLC (A) Rt = 2.60 minutes; m/z $[M+H]^+$ = 505

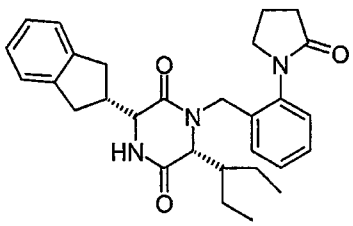
^{1}H NMR ($CDCl_3$) 10.14 (s, 1H); 8.05 (d, 2H); 7.33 (t, 1H); 7.30 – 7.14 (m, 5H); 7.10 (t, 1H); 6.47 (s, 1H); 5.16 (d, 1H); 4.08 (m, 3H); 3.15 (m, 3H); 2.93 (m, 1H); 2.80 (m, 3H); 2.67 (t, 2H); 2.40 (s, 6H); 1.83 (m, 2H); 1.68 (m, 2H); 1.57 (m, 1H); 1.03 (t, 3H); 0.92 (t, 3H).

Examples 120-121 were prepared by methods analogous to that described for Example 119

Ex No	Structure	Mwt	Rt/min	+ve; -ve	Name
120		518.7	2.62 (A)	519; 517	*N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-phenyl)-4-(dimethylamino)butanamide formate
121		530.7	2.64 (A)	531; 529	*N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-1-methyl-4-piperidinecarboxamide formate

Example 122

(3*R*,6*R*)-3-(2,3-Dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(2-oxo-1-pyrrolidinyl)-phenyl]methyl}-2,5-piperazinedione



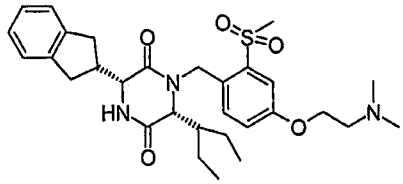
Potassium carbonate (126mg), cuprous iodide (18mg), (1*R*,2*R*)-(-)-N,N'-dimethylcyclohexane-1,2-diamine (48mg), 2-pyrrolidinone (62mg) and (3*R*,6*R*)-1-[(2-bromophenyl)methyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (Ex. 30) (200mg, 0.42mmol) and dioxan (0.4ml) were sequentially added to a 2ml microwave tube. The mixture was heated with stirring at 150C for 4000seconds in a microwave (Emrys™ Optimizer). The reaction mixture was diluted with dichloromethane and purified on an SPE cartridge (5g, silica) eluting with methanol: dichloromethane (0 to 3%). The relevant fractions were evaporated *in vacuo* and further purified on a 2g SCX-SPE cartridge eluting with dichloromethane then methanol. Evaporation of the methanol *in vacuo* and freeze drying from dioxan gave (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(2-oxo-1-pyrrolidinyl)phenyl]methyl}-2,5-piperazinedione as a white lyophilate (27mg).

HPLC (A) Rt = 3.14 minutes; m/z $[M+H]^+$ = 474

^{1}H NMR ($CDCl_3$) δ 7.3 (m, 3H), 7.20 (m, 3H), 7.14 (m, 2H), 5.18 (d, 1H), 4.05 (d, 1H), 4.04 (d, 1H), 3.94 (d, 1H), 3.83 (m, 1H), 3.75 (m, 1H), 3.12 (d, 3H), 2.86 (m, 2H), 2.58 (t, 2H), 2.25 (m, 3H), 1.71 (m, 1H), 1.59 (m, 3H), 1.29 (m, 1H), 0.92 (t, 3H), 0.88 (t, 3H).

Example 123

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[4-{[2-(dimethylamino)ethyl]oxy}-2-(methylsulfonyl)phenyl]methyl}-6-(1-ethylpropyl)-2,5-piperazinedione

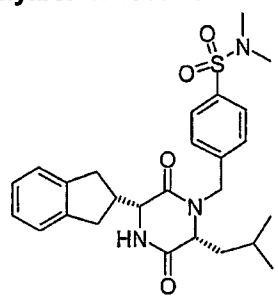


2-{[4-(Aminomethyl)-3-(methylsulfonyl)phenyl]oxy}-*N*,*N*-dimethylethanamine (Int. 11)(0.42g) and 2-ethylbutanal (0.20mL) were dissolved in 2,2,2-trifluoroethanol (10mL). Triethylamine (0.20mL) was then added, and the mixture was stirred overnight then (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]carbonyl} amino)ethanoic acid (0.45g) and 4-chlorophenylisonitrile were added and the mixture was stirred for 3 days. The mixture was dissolved in methanol at 0°C and acetyl chloride (1.7mL) was added. It was then stirred for 1 hour, but LCMS showed no loss of the Boc group, so acetyl chloride (a further 1.7mL) was added and the solution was stirred overnight. The mixture was concentrated under reduced pressure and dissolved in chloroform (20mL). This solution was stirred with aqueous sodium hydrogen carbonate (20mL) for 1 hour. The organic phase was separated and the aqueous phase was extracted twice with chloroform. The organic extracts were concentrated under reduced pressure then dissolved again in chloroform (20mL). Acetic acid (12mL) was added and the mixture was stirred overnight. The mixture was concentrated under reduced pressure to give a yellow solid which was purified using an SPE cartridge followed by mass-directed autoprep and finally by reverse-phase HPLC to give the title compound as a solid

^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1H), 7.46 (d, 1H), 7.41 (s, 1H), 7.24-7.14 (m, 4H), 6.89 (s, 1H), 5.11 (d, 1H), 4.51-4.41 (m, 2H), 4.26 (d, 1H), 4.07-3.95 (m, 2H), 3.72-3.46 (m, 2H), 3.18-3.04 (m, 5H), 2.98 (s, 6H), 2.94-2.73 (m, 3H), 1.76-1.52 (m, 4H), 1.43-1.30 (m, 1H), 1.00-0.87 (m, 6H)

Example 124

4-{[(3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-N,N-dimethylbenzenesulfonamide



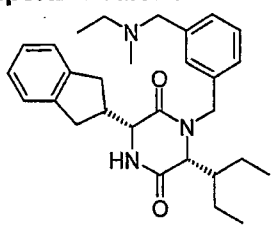
To a solution of 4-(aminomethyl)-N,N-dimethylbenzenesulfonamide (467 mg) in methanol (10 ml) was added (2R)-2,3-dihydro-1H-inden-2-yl({[(1,1-dimethylethyl)-oxy]carbonyl}amino)ethanoic acid (640mg), 2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-phenyl isocyanide (515 mg) and then 3-methylbutanal (0.24 ml). The reaction was then

stirred for 18 hours. The reaction was then cooled to 0°C and treated with acetyl chloride (0.94 ml) and left to warm to ambient temperature overnight. The reaction was concentrated and the residue partitioned between chloroform (10 ml) and sodium bicarbonate (10 ml) and stirred at room temperature for 72 hours. The organic was collected and the aqueous extracted with further chloroform. The combined organics were then concentrated and the residue dissolved in methanol and passed through a SCX SPE and eluted in methanol. The methanol was concentrated to yield a residue which was purified by Redisep (12g) column to give the title compound as a yellow solid, 290 mg.

LCMS (A) Rt = 3.24 minutes; m/z $[M+H]^+$ = 484; m/z $[M-H]^-$ = 482

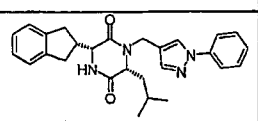
Example 125

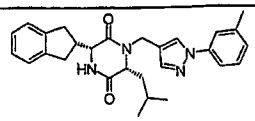
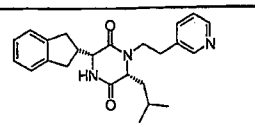
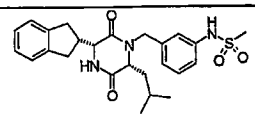
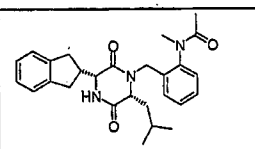
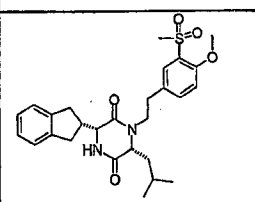
(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-[(3-{[ethyl(methyl)amino]methyl}phenyl)-methyl]-6-(1-ethylpropyl)-2,5-piperazinedione



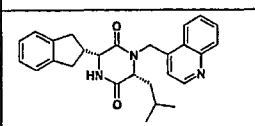
A mixture of *N*-{[3-(aminomethyl)phenyl]methyl}-*N*-methylethanamine (0.2 mmol) and 2-ethylbutanal (0.2 mmol) in methanol (1 ml) was treated with diisopropylethylamine (0.3 mmol) then a solution of (2R)-2,3-dihydro-1H-inden-2-yl({[(1,1-dimethylethyl)oxy] carbonyl}amino)ethanoic acid (0.2 mmol) in methanol (1 ml) and then with a solution of 2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}phenyl isocyanide (0.2 mmol) in methanol (1 ml). The reaction was then stirred for 2 days. The reaction was then cooled to 0°C and treated with acetyl chloride (200 ul) and left to warm to ambient temperature overnight. The reaction was concentrated and the residue partitioned between chloroform and sodium bicarbonate and heated to 50°C for 4 hours. The organic was collected and concentrated and the residue purified by Autoprep HPLC (10-35% CH_3CN). Concentration of the appropriate fractions yielded the title compound as a gum, 10.5 mg.
LCMS (A) Rt = 2.6 minutes; m/z $[M+H]^+$ = 462

The following Examples were prepared by methods analogous to that described for Example 124

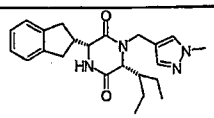
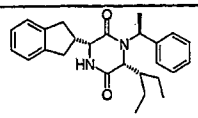
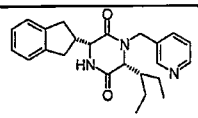
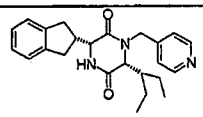
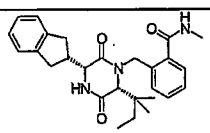
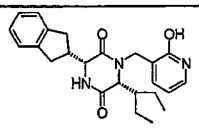
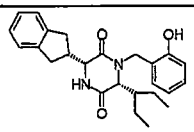
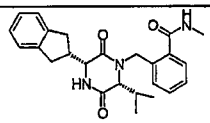
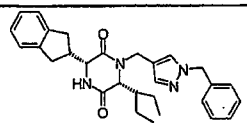
Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
126		442.6	3.32 (A)	443; 441	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-[(1-phenyl-1H-pyrazol-4-yl)methyl]-2,5-piperazinedione

127		456.6	3.44 (A)	457; 455	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-{[1-(3-methylphenyl)-1H-pyrazol-4-yl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione
128		391.5	2.61 (A)	392; 390	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-[2-(3-pyridinyl)ethyl]-2,5-piperazinedione
129		469.6	3.09 (A)	470; 468	N-(3-{[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-methanesulfonamide
130		447.6	3.01 (A)	448; 446	N-(2-{[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-phenyl)-N-methylacetamide
131		498.6	3.18 (A)	499; 497	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-{2-[4-(methyloxy)-3-(methylsulfonyl)phenyl]ethyl}-6-(2-methylpropyl)-2,5-piperazinedione

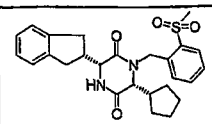
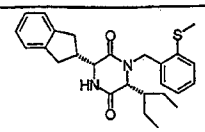
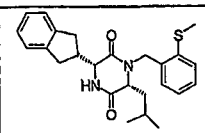
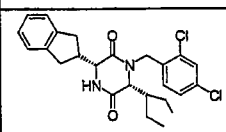
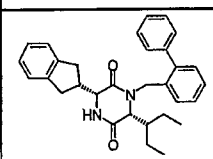
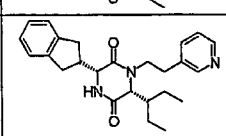
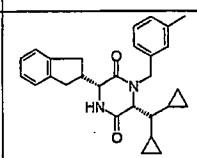
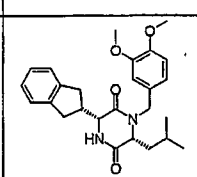
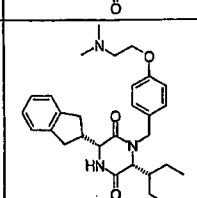
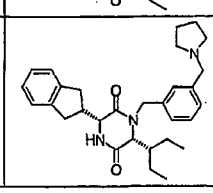
The following Example was prepared by a method analogous to that described for Example 125

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
132		427.5	3.1 (A)	428; 426	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-(4-quinolinylmethyl)-2,5-piperazinedione

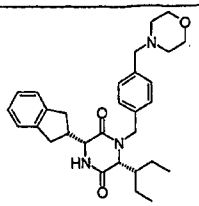
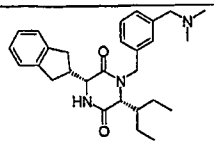
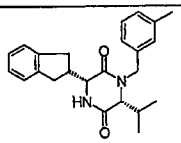
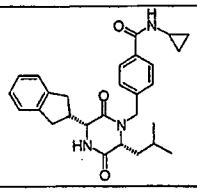
The following Examples were prepared by methods analogous to that described for Example 1, optionally with the addition of a base such as triethylamine or DIPEA if the hydrochloride salts of amines were used.

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
133		394.5	2.99 (A)	395; 393	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-[(1-methyl-1H-pyrazol-4-yl)methyl]-2,5-piperazinedione
134		404.5	3.62 (A)	405; -	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-[(1S)-1-phenylethyl]-2,5-piperazinedione
135		391.5	2.90 (A)	392; 390	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-(3-pyridinylmethyl)-2,5-piperazinedione
136		391.5	2.90 (A)	392; 390	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-(4-pyridinylmethyl)-2,5-piperazinedione
137		447.6	3.04 (A)	448; 446	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1,1-dimethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide
138		407.5	2.91 (A)	408; 406	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-oxo-1,2-dihydro-3-pyridinyl)methyl]-2,5-piperazinedione
139		406.5	3.5 (A)	407; 405	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-hydroxyphenyl)methyl]-2,5-piperazinedione
140		419.5	2.85 (A)	420; 418	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide
141		470.6	3.42 (A)	471; 515	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[1-(phenylmethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione

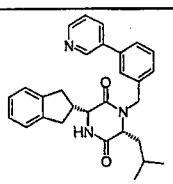
104

142		466.6	3.24 (A)	467; 465	(3*R*,6*R*)-6-cyclopentyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione
143		436.6	3.51 (A)	437; Not seen	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylthio)phenyl]methyl}-2,5-piperazinedione
144		422.6	3.6 (A)	423; 421	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylthio)phenyl]methyl}-2,5-piperazinedione
145		459.4	3.42 (D)	459	(3R,6R)-1-[(2,4-dichlorophenyl)-methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
146		466.6	3.79 (A)	467	(3*R*,6*R*)-1-(2-biphenylylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
147		405.5	2.78 (A)	406	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2-(3-pyridinyl)ethyl]-2,5-piperazinedione
148		428.6	3.55 (A)	429	(3*R*,6*R*)-6-(dicyclopropylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione
149		436.5	3.19 (A)	437	(3*R*,6*R*)-1-{[3,4-bis(methyloxy)-phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methyl-propyl)-2,5-piperazinedione
150		477.7	2.63 (A)	478	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(4-{[2-(dimethylamino)-ethyl]oxy}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione
151		473.7	2.69 (A)	474	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(1-pyrrolidinylmethyl)phenyl]methyl}-2,5-piperazinedione

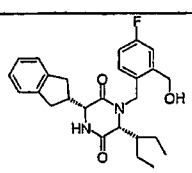
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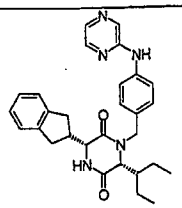
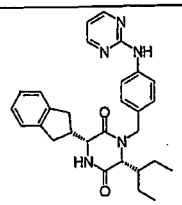
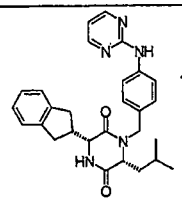
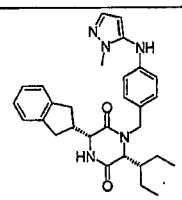
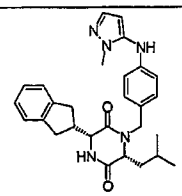
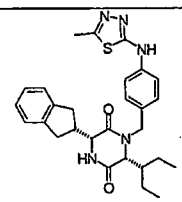
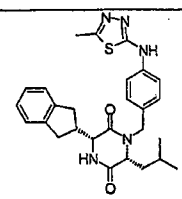
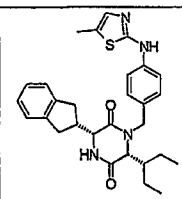
152		489.7	2.51 (A)	490	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinylmethyl)phenyl]methyl}-2,5-piperazinedione
153		447.6	2.57 (A)	448	formic acid - (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({3-[(dimethylamino)methyl]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione (1:1)
154		376.5	3.36 (A)	377	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione
155		459.6	3.15 (A)	460	*N*-cyclopropyl-4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzamide

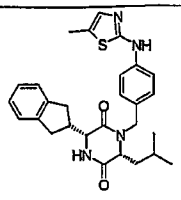
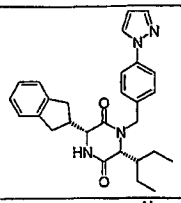
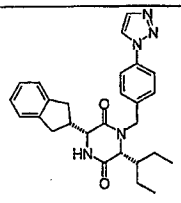
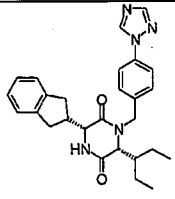
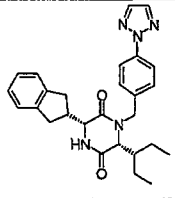
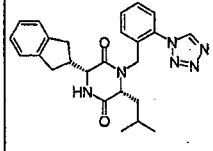
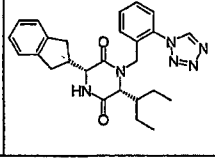
The following Example was prepared by a method analogous to Example 125 starting from Intermediate 12

Ex No	Structure	Mwt	Rt/ min	+ve; -ve	Name
156		453.6	3.2 (A)	454; 452	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-{[3-(3-pyridinyl)phenyl]methyl}-2,5-piperazinedione

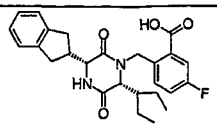
The following Examples were prepared by methods analogous to that described for Example 1 using the intermediates indicated, optionally with the addition of a base such as triethylamine or DIPEA if the hydrochloride salts of amines were used

Ex No	Int No	Structure	Mwt	Rt/ min	+ve; -ve	Name
157	13		438.5	3.39 (A)	439; 484	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-fluoro-2-(hydroxymethyl)-phenyl]methyl}-2,5-piperazinedione

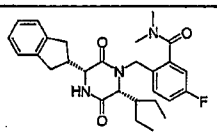
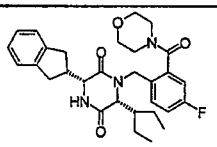
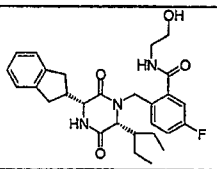
158	23		483.6	0.81 (B)	484	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(pyrazin-2-yl)aminophenyl]-methyl}-2,5-piperazinedione
159	24		483.6	0.8 (B)	484	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(pyrimid-2-yl)aminophenyl]-methyl}-2,5-piperazinedione
160	24		469.6	0.78 (B)	470	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(pyrimid-2-yl)amino-phenyl]methyl}-2,5-piperazinedione
161	25		485.6	0.74 (B)	486	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(1-methyl-1*H*-pyrazol-5-yl)amino]phenyl}methyl)-2,5-piperazinedione
162	25		471.6	0.72 (B)	472	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-({4-[(1-methyl-1*H*-pyrazol-5-yl)amino]phenyl}methyl)-2,5-piperazinedione
163	26		503.7	0.78 (B)	504	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(5-methyl-1,3,4-thiadiazol-2-yl)aminophenyl]methyl}-2,5-piperazinedione
164	26		489.6	0.76 (B)	490	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(5-methyl-1,3,4-thiadiazol-2-yl)aminophenyl]methyl}-2,5-piperazinedione
165	27		502.7	0.73 (B)	503	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(5-methyl-1,3-thiazol-2-yl)aminophenyl]methyl}-2,5-piperazinedione

166	27		488.7	0.69 (B)	489	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(5-methyl-1,3-thiazol-2-yl)aminophenyl]methyl}-2,5-piperazinedione
167	32		456.6	0.87 (B)	457	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-pyrazol-1-yl)phenyl]-methyl}-2,5-piperazinedione
168	30		457.6	0.79 (B)	458	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-1,2,3-triazol-1-yl)-phenyl]methyl}-2,5-piperazinedione
169	33		457.6	0.78 (B)	458	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-1,2,4-triazol-1-yl)-phenyl]methyl}-2,5-piperazinedione
170	31		457.6	0.88 (B)	458	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(2*H*-1,2,3-triazol-2-yl)-phenyl]methyl}-2,5-piperazinedione
171	37		444.5	0.76 (B)	445	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(1*H*-tetrazol-1-yl)phenyl]methyl}-2,5-piperazinedione
172	37		458.6	0.79 (B)	459	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(tetrazol-1-yl)phenyl]-methyl}-2,5-piperazinedione

Example 173 was prepared from Example 157 by methods analogous to those described for Intermediate 51 and Example 65, without isolation of the intermediate aldehyde.

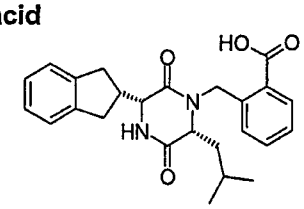
Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
173		452.5	3.6 (A)	453; 451	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-fluorobenzoic acid

The following Examples were prepared from Example 173 by methods analogous to that described for Example 66, except using diisopropylethylamine as the base in place of triethylamine.

Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
174		479.5	3.34 (A)	480 524	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-fluoro-*N*,*N*-dimethylbenzamide
175		521.6	3.25 (A)	522 566	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-fluoro-2-(4-morpholinylcarbonyl)phenyl]-methyl}-2,5-piperazinedione
176		495.5	2.96 (A)	496 494	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-fluoro-*N*-(2-hydroxyethyl)benzamide

Example 177

2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid



(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-1-{[2-(hydroxymethyl)phenyl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione (Int. 14) (1.488 g, 3.66 mmol) was stirred in acetonitrile (8 ml), water (12 ml) and ethyl acetate (12 ml). Sodium periodate (3.21 g, 15 mmol) was added to the stirred mixture followed by ruthenium(3+) trichloride hydrate (24mg). The mixture was stirred vigorously for 2.75 hours before it was filtered and the residue washed with ethyl acetate. The filtrate and washings were combined and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 10 ml). The organic phases were combined, dried ($MgSO_4$) and evaporated to leave a brown foam

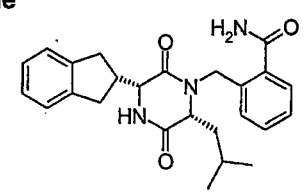
(1.64 g). The brown foam (1.63 g) was stirred in acetonitrile (150 ml) and a solution of sulfamic acid (426 mg, 4.38 mmol) in water (15 ml) was added dropwise, followed after 3 minutes by the dropwise addition of a solution of sodium chlorite (430 mg, 4.75 mmol) in water (15 ml). After the mixture had been stirred at room temperature for 2 hours it was left to stand at room temperature overnight (16.33 hours) before it was evaporated under reduced pressure to remove the organic solvent. The aqueous residue was partitioned between ethyl acetate (100ml) and water (10ml). The organic phase was washed with saturated aqueous sodium chloride solution (25 ml), dried ($MgSO_4$), evaporated under reduced pressure and dried *in vacuo* to afford 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid as an orange / brown foam (1.608g). A portion of 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid was purified further by mass directed autoprep to afford a white solid (45 mg).

LCMS (A) Rt = 3.22 minutes; m/z $[M+H]^+$ = 421

^1H NMR ($CDCl_3$) δ 8.36 (br s, 1H), 8.05 (d, 1H), 7.55 (t, 1H), 7.39 (t, 1H), 7.33 (d, 1H), 7.22 (m, 2H), 7.16 (m, 2H), 5.49 (d, 1H), 4.71 (d, 1H), 4.14 (dd, 1H), 3.93 (dd, 1H), 3.14 (m, 3H), 2.90 (m, 2H), 1.93 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 0.91 (t, 6H).

Example 178

2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzamide



2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid (Ex. 177) (600 mg, 1.26 mmol) was dissolved in dry dichloromethane (9 ml) and triethylamine (353.4 ul, 2.53 mmol) under nitrogen. 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (488 mg, 1.52 mmol) was added to the mixture, which was stirred for 6 hours at room temperature before it was split into 4 and each portion treated with an amine.

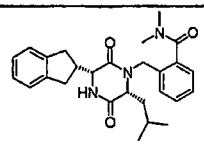
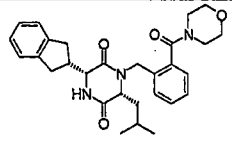
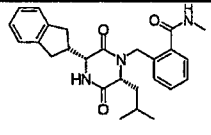
To one portion was added a 2M solution of ammonia in methanol (1 ml, 2 mmol). The mixture was left to stand at room temperature over the weekend, before it was diluted with dichloromethane (2ml) and washed with 1M hydrochloric acid (2 ml) followed by saturated aqueous sodium bicarbonate solution (2 ml). The phases were separated using a hydrophobic frit and the organic phase blown down under nitrogen to leave a brown foam. The foam was purified by mass directed autoprep to afford 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-benzamide (47 mg) as a white solid.

LCMS (A) Rt = 2.94 minutes; m/z $[M+H]^+$ = 420

110

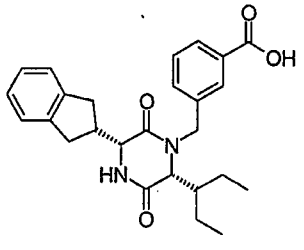
^{1}H NMR ($CDCl_3$) δ 8.15 (br s, 1H), 7.47 (d, 1H), 7.38 (br t, 1H), 7.31 (d, 1H), 7.24 (t, 1H), 7.16 (m, 4H), 6.77 (br s, 2H), 5.42 (d, 1H), 4.28 (d, 1H), 4.03 (m, 1H), 3.91 (m, 1H), 3.06 (m, 3H), 2.82 (m, 2H), 1.92 (m, 1H), 1.73 (m, 2H), 0.93 (d, 6H).

The following Examples were prepared by methods analogous to that described for Example 178

Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
179		477.6	3.08 (A)	448; 446	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*,*N*-dimethylbenzamide
180		489.6	3.08 (A)	490; 488	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione
181		433.6	3.00 (A)	434; 432	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide

Example 182

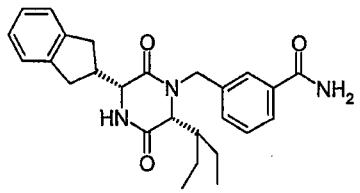
3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoic acid



1,1-Dimethylethyl 3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate (Int. 15) (518 mg, 1.05 mmol) was dissolved in 2M hydrochloric acid in ether (2 ml) and left to stand at room temperature overnight (18.25 hours). Then 4M hydrochloric acid in dioxan (1 ml) was added to the mixture, which was left to stand a further 47 hours before more 4M hydrochloric acid in dioxan (0.4 ml) was added. After a further 5.5 hours the mixture was evaporated under reduced pressure to leave a foam. The foam was dissolved in 4M hydrochloric acid in dioxan (1 ml) and left to stand overnight (22.33 hours) before it was evaporated under reduced pressure to leave a gum, which was evaporated from cyclohexane and dried *in vacuo* to afford 3-

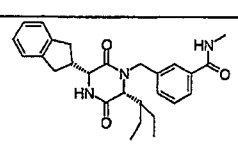
{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-benzoic acid as a pale brown foam (540 mg).
LCMS (A) Rt = 3.3 minutes; m/z $[M+H]^+$ = 435

Example 183
3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzamide

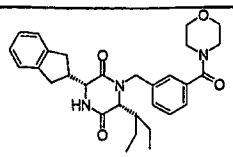


3-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid (Ex. 182) (493 mg, 0.96 mmol) was dissolved in dry dichloromethane (9 ml) under nitrogen and triethylamine (267.2 ul, 1.92 mmol) added. After 5 minutes 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (369 mg, 1.15 mmol) was added to the mixture, which was stirred for 2 hours before being left to stand at room temperature overnight (18.25 hours) and then split into 3 parts and each portion treated with an amine.
To one portion was added a 2M solution of ammonia in methanol (1 ml, 2 mmol). The mixture was left to stand at room temperature for 5 hours before it was diluted with dichloromethane (3ml) and washed with 1M hydrochloric acid (1 ml) followed by saturated aqueous sodium bicarbonate solution (2 ml). The phases were separated using a hydrophobic frit and the organic phase blown down under nitrogen to leave a brown foam. The foam was purified by mass directed autoprep to afford 3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzamide as a pale brown foam (80 mg, 56%).
LCMS (A) Rt = 3.01 minutes; m/z $[M+H]^+$ = 434
^{1}H NMR ($CDCl_3$) δ ? 8.01 (br s, 1H), 7.74 (m, 2H), 7.41 (m, 2H), 7.18 (m, 4H), 6.44 (br s, 2H), 5.35 (d, 1H), 4.10 (m, 2H), 3.93 (d, 1H), 3.14 (m, 3H), 2.88 (m, 2H), 1.73 (m, 1H), 1.66 (m, 1H), 1.58 (m, 2H), 1.31 (m, 1H), 0.92 (t, 3H), 0.87 (t, 3H).

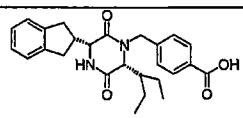
The following Examples were prepared by methods analogous to that described for Example 183

Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
184		447.6	3.05 (A)	448; 446	3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide

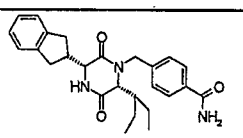
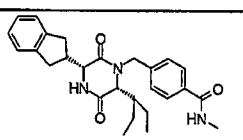
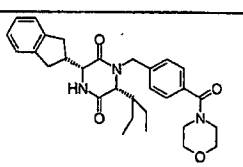
112

185		503.6	3.07 (A)	504; 502	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(4-morpholinylcarbonyl)phenyl]-methyl}-2,5-piperazinedione

The following Example was prepared from Intermediate 54 by a method analogous to that described for Example 182

186		434.5	3.27 (A)	435; 433	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-benzoic acid

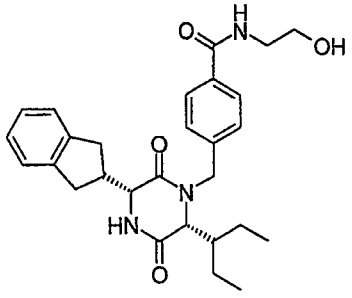
The following Examples were prepared from Example 186 by methods analogous to that described for Example 183

Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
187		433.6	2.98 (A)	434; 432	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-benzamide
188		447.6	3.16 (A)	448; 492	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide
189		503.6	3.1 (A)	504; 502	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazine-dione

Example 190

4-{[(3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-N-(2-hydroxyethyl)benzamide

113

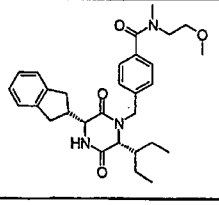


To a solution of the mixed stereoisomers of Intermediate 49 (100 mg, 0.230 mmol) and 2-aminoethanol (30 µL, 0.460 mmol) in CH_2Cl_2 (2 mL) were added diisopropylethylamine (90 µL, 0.506 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarboiimide hydrochloride (EDCI•HCl) (49 mg, 0.253 mmol) and 1-hydroxybenzotriazole hydrate (HOBT) (6 mg, 0.046 mmol). The reaction mixture was stirred at room temperature until judged complete by LCMS. At 16 hours, LCMS indicated about 55% conversion; therefore, additional 2-aminoethanol (10 µL, 0.153 mmol) was added. The reaction mixture was continued to stir for an additional 4 days. LCMS indicated about 65% conversion. The reaction was diluted with EtOAc. The resulting solution was washed with a saturated aqueous $NaHCO_3$ solution and brine. The organics were dried over $MgSO_4$, filtered and concentrated to give 80 mg of a white solid. The crude residue was purified by flash chromatography on silica gel [ISCO, 4 g RediSep® column, CH_2Cl_2 / MeOH 1% - 10%] to give 29 mg of 4-{[(3R,6S)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-N-(2-hydroxyethyl)benzamide (trans-isomer) as an oil and 15 mg of Example 190, 4-{[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-N-(2-hydroxyethyl)benzamide (cis-isomer) as an oil.

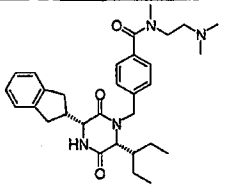
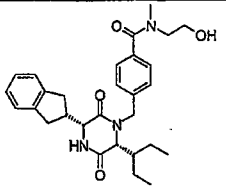
HPLC (B) Rt = 0.71 minutes; m/z $[M+H]^+$ = 478

^1H NMR ($CDCl_3$) δ 7.76 (d, 2H), 7.54 (d, 2H), 7.30 – 7.15 (m, 2H), 7.05 (t, 1H), 5.67 (br s, 1H), 5.33 (d, 1H), 4.07 (m, 2H), 3.89 (d, 1H), 3.82 (t, 2H), 3.62 (m, 2H), 3.15 (m, 3H), 3.0 – 2.75 (m, 2H), 2.54 (br s, 2H), 1.80 – 1.50 (m, 4H), 1.34 (m, 1H), 0.95 (t, 3H), 0.88 (t, 3H).

The following Examples were prepared from Intermediate 49 by methods analogous to that described for Example 190

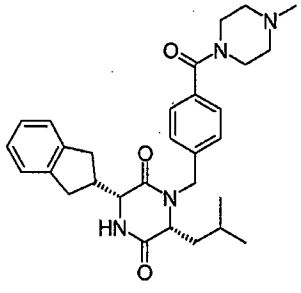
Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
191		505.7	0.78 (B)	506	4-{[(3R,6R)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-N-methyl-N-[2-(methyloxy)-ethyl]benzamide

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192		518.7	0.67 (B)	519	4-{[(3R,6R)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-N-[2-(dimethylamino)ethyl]-N-methylbenzamide
193		491.6	0.72 (B)	492	4-{[(3R,6R)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-N-(2-hydroxyethyl)-N-methylbenzamide

Example 194

(3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-1-({4-[(4-methyl-1-piperazinyl)carbonyl]-phenyl}methyl)-6-(2-methylpropyl)-2,5-piperazinedione



To a solution of the mixed stereoisomers of Intermediate 50 (110 mg, 0.262 mmol) in CH_2Cl_2 (2.3 mL) were added diisopropylethylamine (55 µL, 0.314 mmol), 1-methylpiperizine (32 µL, 0.288 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (119 mg, 0.314 mmol). After stirring at room temperature for 2 hours, LCMS indicated complete conversion. The reaction was diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution and brine. The organics were dried over $MgSO_4$, filtered and concentrated to give 180 mg of an off-white solid. The crude residue was purified by flash chromatography on silica gel [ISCO, 4 g RediSep® column, CH_2Cl_2 / MeOH 1% - 10%] to give 53 mg of (3R,6S)-3-(2,3-dihydro-1H-inden-2-yl)-1-({4-[(4-methyl-1-piperazinyl)carbonyl]phenyl}methyl)-6-(2-methylpropyl)-2,5-piperazinedione (trans-isomer) as a white powder and 41 mg of Example 193, (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-({4-[(4-methyl-1-piperazinyl)-carbonyl]phenyl}methyl)-6-(2-methylpropyl)-2,5-piperazinedione (cis-isomer) as a white powder.

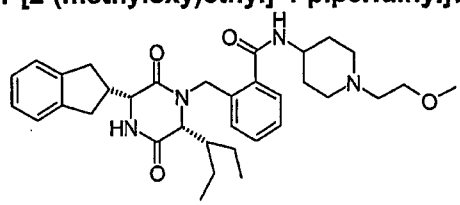
HPLC (B) Rt = 0.62 minutes; m/z $[M+H]^+$ = 503

1H NMR (CDCl3) δ 7.40 (d, 2H), 7.32 (d, 2H), 7.28 – 7.15 (m, 4H), 5.36 (d, 1H), 4.07 (dd, 1H), 3.94 (d, 1H), 3.81 (m, 3H), 3.47 (br s, 2H), 3.12 (m, 3H), 2.86 (m, 2H), 2.60 – 2.30 (m, 4H), 2.36 (s, 3H), 1.97 (m, 1H), 1.83 (m, 1H), 1.66 (m, 1H), 0.97 (t, 6H).

Example 195

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2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-{1-[2-(methyloxy)ethyl]-4-piperidinyl}benzamide



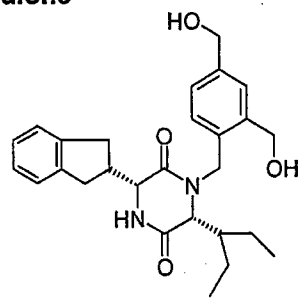
To a stirred solution of 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-4-piperidinylbenzamide (Example 83) (101 mg, 0.2 mmol) in anhydrous dimethylformamide (2 ml) was added potassium carbonate (27 mg, 0.2 mmol) and 2-bromoethylmethylether (20.2 uL, 0.21 mmol). The reaction was stirred for 20 hours. Further potassium carbonate (13.5 mg, 0.1 mmol) and 2-bromoethylmethyl-ether (15 uL, 0.16 mmol) were added and the reaction was stirred for 2.5 hours before more 2-bromoethylmethylether (15 uL, 0.16 mmol) was added. Then the reaction was stirred at room temperature over the weekend (71 hours) before further 2-bromoethyl-methylether (15 uL, 0.16 mmol) was added. Then the reaction was stirred for 25.5 hours before further potassium carbonate (16 mg, 0.11 mmol) and 2-bromoethylmethylether (15 uL, 0.16 mmol) were added and the reaction was stirred for 18 hours. The reaction mixture was partitioned between dichloromethane (10 ml) and saturated aqueous ammonium chloride (5ml). The aqueous phase was extracted with dichloromethane (4 ml). The phases were separated using a hydrophobic frit. The combined organic phase was evaporated under reduced pressure to give a pale orange solid. The solid in a small volume of dichloromethane was loaded onto an SCX –SPE column, washed with methanol then eluted with 2M ammonia/methanol. Concentration gave a pale cream foam, which was loaded onto a 12g flash silica chromatography column (pre-eluted with 0.4% triethylamine in ethyl acetate). The column was eluted with 0% to 100% solvent B in solvent A (solvent A = 0.4% triethylamine in ethyl acetate, and solvent B = 20% ethanol in ethyl acetate) to afford 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-{1-[2-(methyloxy)ethyl]-4-piperidinyl}-benzamide as a white solid (68 mg, 60%).

LCMS (A) Rt = 2.64 minutes; m/z $[M+H]^+$ = 575

^{1}H NMR ($CDCl_3$) δ 7.54 (br d, 1H), 7.43 (br d, 1H), 7.38 (br t, 1H), 7.30 (br t, 1H), 7.24 (m, 2H), 7.17 (m, 3H), 6.78 (d, 1H), 5.11 (d, 1H), 4.43 (d, 1H), 4.12 (d, 1H), 4.03 (dd, 1H), 3.98 (m, 1H), 3.52 (t, 2H), 3.36 (s, 3H), 3.11 (m, 3H), 2.92 (m, 3H), 2.81 (m, 1H), 2.59 (t, 2H), 2.23 (m, 2H), 2.05 (m, 2H), 1.77 -1.53 (m, 6H), 1.35 (m, 1H), 0.96 (t, 3H), 0.90 (t, 3H).

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Example 196
(3*R*,6*R*)-1-{[2,4-Bis(hydroxymethyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione



[4-(Aminomethyl)benzene-1,3-diyl]dimethanol (2.22 g, 13.3 mmol) and (2*R*)-2,3-dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethanoic acid (3.87 g, 13.3 mmol) were dissolved in 15 mL methanol. 2-Ethylbutanal (1.33 g, 13.3 mmol) were added into the solution. The resulting solution was stirred at room temperature for 30 minutes. Then 4-chlorophenyl isocyanide (1.44 g, 13.3 mmol) was added and the resulting mixture was stirred at room temperature for 1 hour. The solvent was removed in vacuo. The residue was redissolved in 20 mL chloroform and cooled to 0°C. The cold solution was then treated with 4M HCl in dioxane. The resulting mixture was then warmed up to room temperature and stirred overnight. The solvent was then removed and redissolved in 150 mL chloroform. The solution was then washed with 30 mL saturated sodium bicarbonate. The aqueous solution was extracted with 2 x 30 mL chloroform. The combined organics were dried over magnesium sulfate and concentrated. The resulting residue was redissolved in 30 mL chloroform. The solution was treated with 1.5 mL acetic acid and stirred at room temperature overnight. The solution was then concentrated. The residue was purified via silica gel chromatography eluting with 50-100% ethyl acetate in hexanes to give (3*R*,6*R*)-1-{[2,4-bis(hydroxymethyl)phenyl] methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (1.05 g, 17%) as an off-white solid.

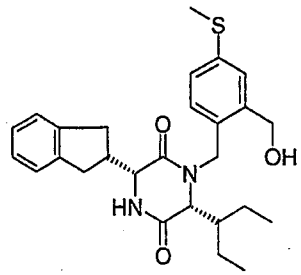
LCMS (B) Rt = 0.71 minutes; m/z $[M+H]^+$ = 451

^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1H), 7.16-7.27 (m, 5H), 7.02 (s, 1H), 5.45 (d, 1H), 4.69 (d, 1H), 4.66 (s, 2H), 4.57 (d, 1H), 4.10 (d, 1H), 3.94-4.05 (m, 2H), 3.09-3.14 (m, 2H), 2.87-2.89 (m, 1H), 2.77-2.80 (m, 1H), 2.30 (bs, 3H), 1.70-1.80 (m, 1H), 1.51-1.68 (m, 3H), 1.20-1.30 (m, 1H), 0.80-0.90 (m, 6H).

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Example 197

((3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylthio)phenyl]methyl}-2,5-piperazinedione



(2*R*)-2,3-Dihydro-1*H*-inden-2-yl({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethanoic acid (0.80 g, 2.73 mmol), [2-(aminomethyl)-5-(methylthio)phenyl]methanol (0.50 g, 2.73 mmol) and 2-ethylbutanal (0.36 mL, 2.73 mmol) were dissolved in 10 mL methanol. The resulting solution was stirred at room temperature for 30 minutes. Then 4-chlorophenyl isocyanide (0.30 g, 2.73 mmol) was added and the resulting mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The residue was then purified via isco silica gel chromatography eluting with 10-100% dichloromethane in hexanes to give 1,1-dimethylethyl [(1*R*)-2-((1-{[(4-chlorophenyl)amino]carbonyl}-2-ethylbutyl){[2-(hydroxymethyl)-4-(methylthio)phenyl]methyl}amino)-1-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethyl]carbamate (1.26 g, 67%) as a white solid. This material (0.86 g, 1.24 mmol) was treated with 4 M hydrochloride in dioxane solution (12.4 mL, 2.48 mmol) at room temperature for 2 hours, then was placed in -20 °C freezer for 72 hours. After warming up to room temperature for 2 hours, the solvent was then removed and redissolved in 15 mL chloroform. The solution was then stirred with 10 mL saturated sodium bicarbonate for 20 minutes. The phases were seperated. The aqueous solution was extracted with 2 x 15 mL chloroform. The combined organics were dried over magnesium sulfate and concentrated. The resulting residue was redissolved in 15 mL chloroform. The solution was treated with 0.75 mL 20% v/v acetic acid in dioxane and stirred at room temperature overnight. The solution was then concentrated. The residue was then redissolved in 50 mL ethyl acetate and washed with 15 mL saturated sodium bicarbonate solution. The organic phase was drive over magnesium sulfate and concentrated. The residue was purified via isco silica gel chromatography eluting with 30-70% ethyl acetate in hexanes to give (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylthio)phenyl]methyl}-2,5-piperazinedione (0.17 g, 30%) as an white solid.

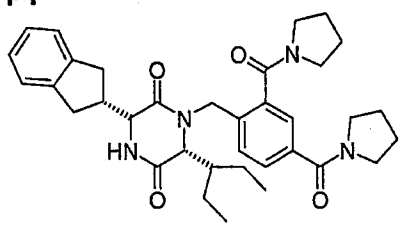
LCMS (D) Rt = 2.89 minutes; m/z $[M+H]^+$ = 467

^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1H), 7.20-7.35 (m, 3H), 7.13-7.17 (m, 3H), 5.25 (d, 1H), 4.61 (dd, 2H), 4.36 (d, 1H), 4.11-4.13 (m, 1H), 3.92 (d, 1H), 3.09-3.11 (m, 3H), 2.88-2.91 (m, 2H), 2.50 (s, 3H), 1.72-1.82 (m, 1H), 1.60-1.65 (m, 3H), 1.20-1.35 (m, 1H), 0.92 (t, 3H), 0.89 (t, 3H).

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Example 199

(3*R*,6*R*)-1-{[2,4-Bis(1-pyrrolidinylcarbonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione

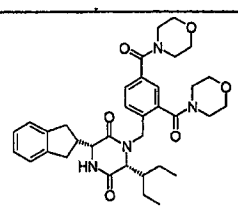
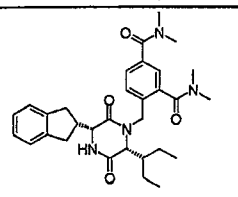


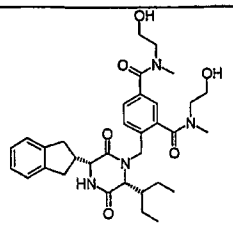
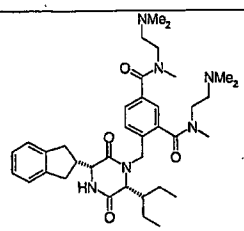
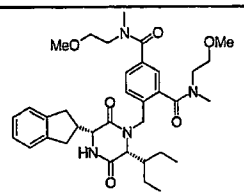
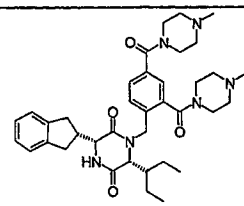
4-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-1,3-benzenedicarboxylic acid (Int. 52) (50 mg, 0.105 mmol), HATU (99.4 mg, 0.262 mmol) and pyrrolidine (17.9 mg, 0.251 mmol) were dissolved in 1 mL dichloromethane. diisopropylethylamine (54.1 mg, 0.418 mmol) was then added. The resulting solution was stirred at RT for one hour. The crude reaction mixture was then purified via Gilson HPLC eluting with 0.1% trifluoroacetic acid in acetonitrile / water. The product containing fractions were combined and concentrated. The residue was redissolved in 20 mL ethyl acetate, washed with 5 mL saturated sodium bicarbonate, dried over $MgSO_4$ and concentrated to give (3*R*,6*R*)-1-{[2,4-bis(1-pyrrolidinyl-carbonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (30 mg, 49%) as a white solid.

LCMS (B) Rt = 0.77 minutes; m/z $[M+H]^+$ = 585.4

^1H NMR ($CDCl_3$) δ 7.49 (d, 1H), 7.47 (s, 1H), 7.29 (d, 1H), 7.19 (m, 2H), 7.14 (m, 2H), 5.06 (d, 1H), 4.24 (d, 1H), 3.99 (s, 1H), 3.97 (d, 1H), 3.59 (t, 4H), 3.36-3.41 (m, 4H), 3.06-3.27 (m, 4H), 1.80-2.00 (m, 8H), 1.48-1.70 (m, 4H), 1.20-1.30 (m, 2H), 0.80-0.90 (m, 6H).

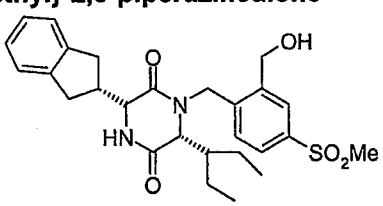
The following Examples were prepared by methods analogous to that described for Example 199

Ex No	Structure	Mwt	Rt/ min	+ve	Name
200		616.8	0.72 (B)	617	(3*R*,6*R*)-1-{[2,4-bis(4-morpholinylcarbonyl)phenyl]-methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione
201		532.7	0.73 (B)	533	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*,*N*,*N'*,*N'*-tetramethyl-1,3-benzenedicarboxamide

202		592.7	0.66 (B)	593	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*,*N*'-bis(2-hydroxyethyl)-*N*,*N*'-dimethyl-1,3-benzene-dicarboxamide
203		646.9	0.58 (B)	647	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*,*N*'-bis[2-(dimethylamino)ethyl]-*N*,*N*'-dimethyl-1,3-benzene-dicarboxamide
204		620.8	0.75 (B)	621	4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*,*N*'-dimethyl-*N*,*N*'-bis[2-(methyloxy)-ethyl]-1,3-benzene-dicarboxamide
205		641.9	0.57 (B)	643	(3*R*,6*R*)-1-({2,4-bis[(4-methyl-1-piperazinyl)carbonyl]phenyl}methyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione

Example 206

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione



((3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylthio)phenyl]methyl}-2,5-piperazinedione (Example 197) (167 mg, 0.36 mmol) was treated with 30% hydrogen peroxide (0.16 mL, 1.44 mmol) and 1 mL acetic acid at 80°C for 6 hours. The solvent was then removed. The crude material was purified via combiflash silica gel column eluting with 0-5% Methanol in dichloromethane to give (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione (0.133 g, 75%) as a white solid.

LCMS (B) Rt = 0.73 minutes; m/z $[M+H]^+$ = 499

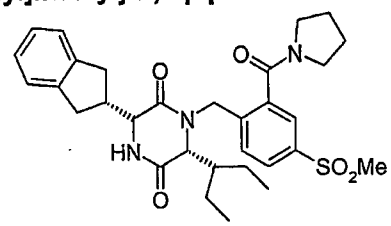
^{1}H NMR (CD_3OD) δ 8.08 (s, 1H), 7.92 (d, 1H), 7.47 (d, 1H), 7.19 (m, 2H), 7.12 (m, 2H), 5.28 (d, 1H), 4.78 (dd, 2H), 4.52 (d, 1H), 4.41 (d, 1H), 4.00 (d, 1H), 3.26-3.33 (m, 1H),

120

3.16 (d, 1H), 3.10-3.16 (m, 1H), 3.00 (dd, 2H), 2.90 (dd, 1H), 1.87 (m, 1H), 1.66 (m, 3H), 1.30-1.41 (m, 1H), 0.90-1.00 (m, 6H).

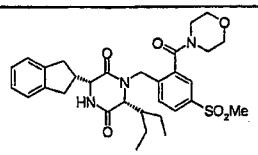
Example 208

(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)-2-(1-pyrrolidinylcarbonyl)phenyl]methyl}-2,5-piperazinedione

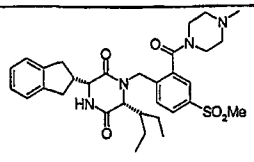
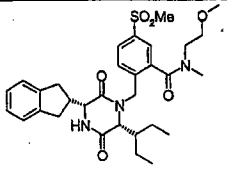
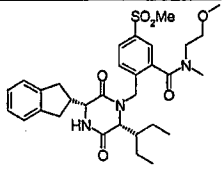
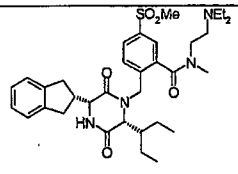
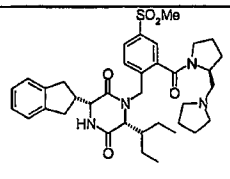


2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-5-(methylsulfonyl)benzoic acid (Int. 53) (50 mg, 0.097 mmol), HATU (48.0 mg, 0.126 mmol) and pyrrolidine (16 µL, 0.194 mmol) were dissolved in 1 mL acetonitrile. diisopropylethylamine (34 µL, 0.194 mmol) was then added. The resulting solution was stirred at RT until no more starting material was left as monitored by LCMS. The crude reaction mixture was then purified via Gilson HPLC eluting with 0.1% trifluoroacetic acid in acetonitrile / water. The product containing fractions were combined and concentrated. The residue was redissolved in 20 mL ethyl acetate, washed with 5 mL saturated sodium bicarbonate, dried over $MgSO_4$ and concentrated to give (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)-2-(1-pyrrolidinyl-carbonyl)phenyl]methyl}-2,5-piperazinedione (8.8 mg, 16%) as a white solid.
LCMS (B) Rt = 0.77 minutes; m/z $[M+H]^+$ = 566
^1H NMR ($CDCl_3$) δ 7.94 (d, 1H), 7.88 (s, 1H), 7.54 (d, 1H), 7.18-7.26 (m, 4H), 6.74 (d, 1H), 5.02 (d, 1H), 4.42 (d, 1H), 4.12 (d, 1H), 4.05 (dd, 1H), 3.66-3.70 (m, 2H), 3.25-3.31 (m, 1H), 3.10-3.23 (m, 4H), 3.07 (s, 3H), 2.83-2.93 (m, 1H), 2.70-2.80 (m, 1H), 1.90-2.10 (m, 4H), 1.50-1.70 (m, 2H), 1.20-1.40 (m, 2H), 0.97 (t, 3H), 0.90 (t, 3H).

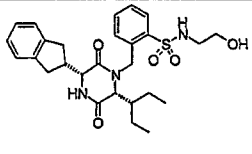
The following Examples were prepared by methods analogous to Example 208

Ex No	Structure	Mwt	Rt/ min	+ve	Name
209		581.7	0.74 (B)	582	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)-2-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione

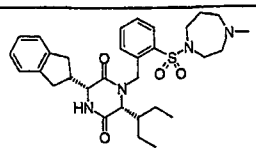
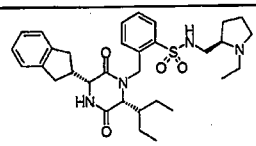
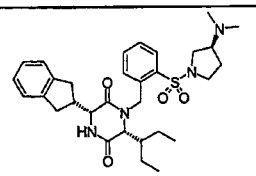
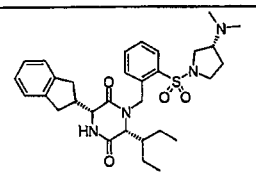
121

210		594.8	0.64 (B)	595	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-[(4-methyl-1-piperazinyl)-carbonyl]-4-(methylsulfonyl) phenyl]methyl}-2,5-piperazine-dione
211		583.8	0.76 (B)	584	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-*N*-[2-(methyloxy)ethyl]-5-(methylsulfonyl)benzamide
211		583.8	0.76 (B)	584	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-*N*-(1-methyl-4-piperidinyl)benzamide
212		624.8	0.67 (B)	625	*N*-[2-(diethylamino)ethyl]-2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-5-(methylsulfonyl)-benzamide
213		648.9	0.68 (B)	649	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-(methylsulfonyl)-2-{[(2*S*)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl}phenyl)methyl]-2,5-piperazinedione

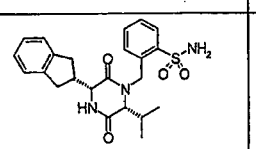
The following Examples were prepared by methods analogous to Example 89.

Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
214		513.7	3.15 (A)	514; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethyl-propyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)benzene-sulfonamide

122

215		566.8	2.70 (A)	567; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methylhexahydro-1*H*-1,4-diazepin-1-yl)-sulfonyl]phenyl}methyl)-2,5-piperazinedione
216		580.8	2.77 (A)	581; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-{[(2*R*)-1-ethyl-2-pyrrolidinyl]methyl}-benzenesulfonamide
217		566.8	2.68 (A)	567; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[(3*S*)-3-(dimethylamino)-1-pyrrolidinyl]sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione
218		566.8	2.74 (A)	567; -	(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[(3*R*)-3-(dimethylamino)-1-pyrrolidinyl]sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione

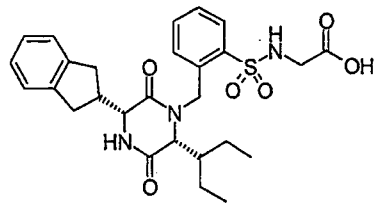
The following Example was prepared by a method analogous to Example 89, starting from Intermediate 47

Ex No	Structure	MW	Rt/ min	+ve ; -ve	Name
219		441	3.0 (A)	442; -	2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-2,5-dioxo-1-piperazinyl]methyl}benzene-sulfonamide

Example 220

***N*-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)sulfonyl]glycine**

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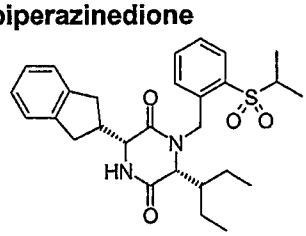
Phenylmethyl N-[(2-{[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo 1-piperazinyl]methyl}phenyl)sulfonyl]glycinate (Int. 16) (60mg) was hydrogenated in ethanol (3mL) at atmospheric pressure in the presence of palladium on carbon (20mol% Pd) and acetic acid (0.5mL). The resulting product was purified by MDAP to give 3mg of pure material.

LCMS (A) Rt = 3.28 minutes; m/z $[M+H]^+$ = 528, $[M]^-$ = 526.

^{1}H NMR δ 8.2 (br.s, 1H), 7.97 (d, 1H), 7.46 (t, 1H), 7.34 (t, 1H), 7.10-7.22 (m, 4H), 6.97 (d, 1H), 6.05 (br.s, 1H), 5.58 (br.d, 1H), 4.88 (br.d, 1H), 4.31 (d, 1H), 3.95 (d, 1H), 3.78 (br.s, 2H), 2.82-3.18 (m, 5H), 1.48-1.73 (m, 3H), 1.27 (m, 1H), 0.86 (m, 6H).

Example 221

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methylethyl)-sulfonyl]phenyl}methyl)-2,5-piperazinedione



(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-mercaptophenyl)-methyl]-2,5-piperazinedione (Int. 19) (100mg) was stirred with 2-iodopropane (26uL) and diisopropylethylamine (45uL) in THF (2mL) for 18 hours then potassium *tert*-butoxide (29mg) was added and the mixture heated to 50°C for 2 hours and reduced *in vacuo*. The resulting residue was dissolved in DCM (2mL) and 3-chloroperoxybenzoic acid (207mg) was added. The mixture was stirred for 48 hours and passed through a 2g aminopropyl SPE column eluting the crude product in methanol (10mL). The eluent was reduced *in vacuo* and purified by MDAP to give 20mg of a white solid.

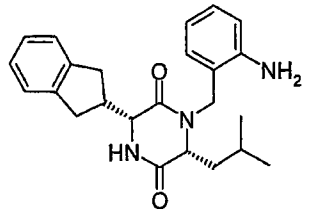
HPLC (A) Rt = 3.42 minutes; m/z $[M+H]^+$ = 496.

^{1}H NMR δ 8.03 (d, 1H), 7.61 (t, 1H), 7.48 (t, 1H), 7.15-7.35 (m, 5H), 6.32 (br.s, 1H), 5.32 (d, 1H), 4.94 (d, 1H), 4.14 (dd, 1H), 4.09 (d, 1H), 3.37 (sex., 1H), 3.15 (m, 2H), 2.98 (sept., 1H), 2.82 (dd, 1H), 1.63 (m ,2H), 1.40 (d, 3H), 1.33 (m, 1H), 1.29 (d, 3H), 0.86 (t, 3H), 0.85 (t, 3H).

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Example 222

(3R,6R)-1-[(2-Aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione

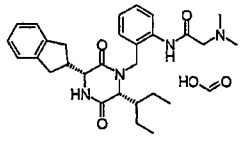


Hydrazine hydrate (0.5g, 10mmol) was added dropwise to a mixture of (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(2-methylpropyl)-1-[(2-nitrophenyl)methyl]-2,5-piperazinedione (Ex. 35) (1.3g) and Raney nickel (0.5g) in THF (20ml). After 1 hour the catalyst was filtered off and the solution concentrated in vacuo to obtain the desired product (1.3g, crude).

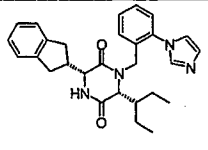
LCMS (D) Rt = 2.63 minutes; m/z $[M+H]^+$ = 392

^{1}H NMR ($CDCl_3$) δ 7.27 – 7.13 (m, 5H), 7.05 (d, 1H), 6.77 – 6.67 (m, 3H), 5.15 (d, 1H), 4.80 (br s, 2H), 4.09 (d, 1H), 4.02 (dd, 1H), 3.91 (dd, 1H), 3.20 – 3.06 (m, 3H), 2.94 – 2.77 (m, 2H), 1.98 (m, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 1.01 (d, 3H), 0.95 (d, 3H).

The following Example was prepared by a method analogous to Example 118

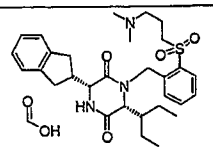
Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
223		490.6	2.56 (A)	491; 489	N^1-(2-{[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-N^2,N^2-dimethylglycinamide formate

The following Example was prepared by a method analogous to Example 122 except no (1*R*,2*R*)-(-)-N,N'-dimethylcyclohexane-1,2-diamine was used

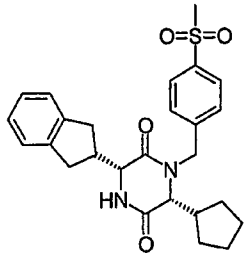
Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
224		456.6	2.72 (A)	457; 455	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1H-imidazol-1-yl)phenyl]-methyl}-2,5-piperazinedione

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The following Example was prepared by a method analogous to Intermediate 21, using N,N-dimethyl-3-chloropropylamine as alkylating agent, and subsequent oxidation by a method analogous to Intermediate 22 without isolation of the intermediate sulfide

Ex No	Structure	MW	Rt/ min	+ve; -ve	Name
225		585.7	2.7 (A)	540; 584	formic acid - (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione (1:1)

Example 226
(3R,6R)-6-Cyclopentyl-3-(2,3-dihydro-1H-inden-2-yl)-1-{[4-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione



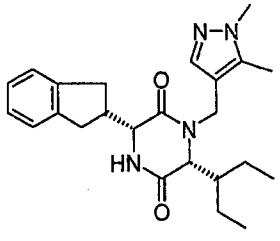
{[4-(Methylsulfonyl)phenyl]methyl}amine hydrochloride (0.85 g, 3.83 mmol) was dissolved in methanol (4 mL) and cyclopentanecarbaldehyde (0.31 mL, 3.83 mmol) added followed by (2R)-2,3-dihydro-1H-inden-2-yl({[(1,1-dimethylethyl)oxy]carbonyl}-amino)ethanoic acid (1.11 g, 3.83 mmol) and diisopropylethyl amine (0.63 mL, 3.61 mmol). The mixture was stirred for 15 minutes before 4-chlorophenylisonitrile (0.52 g, 3.83 mmol) was added. The mixture was stirred for 2.25 hours and then left to stand at room temperature overnight (20 hours) before it was cooled in an ice / water bath. Then acetyl chloride (1.6 mL, 22.80 mmol) was added dropwise, keeping the reaction temperature below 20°C. Then the mixture was stirred in the cooling bath for a further 10 minutes before it was stirred at room temperature. After 18 hours the mixture was evaporated under reduced pressure to leave a dark brown gum. The gum was stirred in chloroform (40 mL) and saturated aqueous sodium bicarbonate solution (40 mL) for 20 minutes before it was diluted with chloroform (40 mL) and the phases separated. The aqueous phase was extracted with chloroform (3 × 40 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chloroform (40 mL) was added to the residue and the resulting solution was treated with glacial acetic acid (1.6 mL) and left to stand, at room temperature over the weekend. Then the reaction mixture was washed with 2M hydrochloric acid (40 mL), followed by saturated aqueous sodium bicarbonate solution (40 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a brown foam. The crude residue was purified by flash

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chromatography on silica gel [Isco, 40g RediSep® column, Hexanes / EtOAc 10% 60%] to give 200 mg of (3R,6R)-6-cyclopentyl-3-(2,3-dihydro-1H-inden-2-yl)-1-{[4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione as an colorless oil.
^{1}H NMR ($CDCl_3$) δ 7.93 (d, 2H), 7.77 (d, 1H), 7.46 (d, 2H), 7.28 – 7.15 (m, 3H), 5.47 (d, 1H), 4.14 (m, 2H), 4.06 (dd, 1H), 3.75 (d, 1H), 3.15 (m, 3H), 3.06 (s, 3H), 2.87 (m, 2H), 2.24 (m, 1H), 2.01 (m, 1H), 1.80 (m, 2H), 1.60 (m, 4H).
HPLC (B) Rt = 0.77 minutes; m/z $[M+H]^+$ = 467.

Example 227

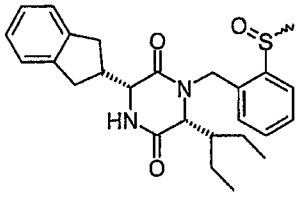
(3R,6R)-3-(2,3-Dihydro-1H-inden-2-yl)-1-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione



[(1,5-Dimethyl-1H-pyrazol-4-yl)methyl]amine hydrochloride was isolated as the free amine by means of an aminopropyl ion exchange column. To a solution of this material (280 mg) and (2R)-2,3-dihydro-1H-inden-2-yl ({[(1,1-dimethylethyl)oxy]carbonyl}amino)-ethanoic acid (580 mg) in methanol (4 ml) was added 2-{[(1,1-dimethylethyl)(dimethyl)-silyl]oxy}phenyl isocyanide (470 mg) followed by 2-ethylbutanal (250 µl) and molecular sieves. The reaction was then stirred overnight. Acetyl chloride (1.43 ml) was then added and the reaction heated at 50°C overnight. The reaction was concentrated and the residue partitioned between chloroform and sodium bicarbonate and heated at 50°C for 6 hours. Triethlyamine (3 eq) was then added and the reaction stirred at room temperature for a week. The organic layer was concentrated in vacuo and the residue purified by MDAP.
LCMS (A) Rt = 3.1 minutes; m/z $[M+H]^+$ = 409.

Examples 228-229

Isomers of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methyl-sulfinyl)phenyl]methyl}-2,5-piperazinedione



(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylthio)phenyl]methyl}-2,5-piperazinedione (Ex. 143) (254 mg, 0.58 mmol) was added to a vigorously stirred suspension of wet alumina (580 mg, for prep see Synlett, 1992, 235) and oxone (357 mg, 0.58 mmol) in dichloromethane (2.9 ml) and the mixture cautiously heated at 40 °C

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and monitored by LCMS until the reaction was deemed complete. The reaction mixture was then filtered and concentrated to yield a white solid which was purified by silica chromatography (SPE, chloroform, dichloromethane, ether, ethylacetate, acetone and methanol) to yield a 2:1 mixture of the sulfoxide epimers as a white solid (160 mg).

A 54 mg portion of this mixture was separated by chiral HPLC (Chiralpak AD, eluent 50% EtOH/ heptane, 15 ml/min) to give:

Example 228, isomer 1 (26 mg) with HPLC retention time = 11.6 min.

LC/MS (A) Rt = 3.15 minutes; m/z $[M+H]^+$ = 453; m/z $[M+formate]^-$ = 497.

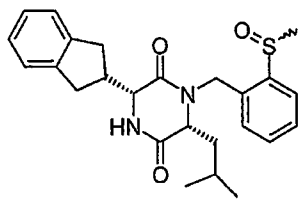
Example 229, isomer 2 (14 mg) with HPLC retention time 18.06 min.

LC/MS (A) Rt = 3.17 minutes; m/z $[M+H]^+$ = 453; m/z $[M+formate]^-$ = 497.

The absolute stereochemistry at sulfur for each of these isomers is currently unknown.

Examples 230-231

Isomers of (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfinyl)phenyl]ethyl}-2,5-piperazinedione were prepared from Ex. 144 by a method analogous to Examples 228-229, using 40% ethanol/heptane as eluent for the chiral separation.



Example 230, isomer 1

LC/MS (A) Rt = 3.05 minutes; m/z $[M+H]^+$ = 439; m/z $[M+formate]^-$ = 482.

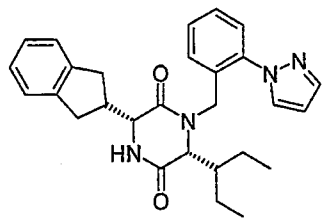
Example 231, isomer 2

LC/MS (A) Rt = 3.07 minutes; m/z $[M+H]^+$ = 439; m/z $[M+formate]^-$ = 482.

The absolute stereochemistry at sulfur for each of these isomers is currently unknown.

Example 232

(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1*H*-pyrazol-1-yl)phenyl]methyl}-2,5-piperazinedione



Potassium carbonate (118mg), cuprous iodide (18mg), pyrazole (58mg), (3R,6R)-1-[(2-bromophenyl)methyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione (Ex. 30) (200mg, 0.4mmol) and NMP (0.5ml) were sequentially added to a 2ml microwave tube. The mixture was heated with stirring at 190°C for 2 hours in a microwave (Emrys™ Optimizer). The reaction mixture was diluted with dichloromethane

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and purified on an SPE cartridge (5g, SCX2) eluting with ammonia/DCM. The relevant fractions were evaporated *in vacuo* to a green oil and further purified on a 5g Si-SPE cartridge eluting with methanol in dichloromethane (0 to 10%). Evaporation of the relevant fraction *in vacuo* gave after freeze drying from dioxan the title compound (100mg) as a cream solid.
LC/MS (A) Rt = 3.41 minutes; m/z $[M+H]^+$ = 457

Example 233 (3*R*,6*R*)-1-[(2,4-difluorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 5.51 min; m/z $[M+H]^+$ = 413; m/z $[M-H]^-$ = 411.
Example 234 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione LCMS (A) Rt = 3.01 min; m/z $[M+H]^+$ = 455; m/z $[M-H]^-$ = 453.
Example 235 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(1*S*)-1-(4-nitrophenyl)ethyl]-2,5-piperazinedione LCMS (A) Rt = 3.43 min; m/z $[M+H]^+$ = 436; m/z $[M-H]^-$ = 434.
Example 236 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(4-nitrophenyl)methyl]-2,5-piperazinedione LCMS (A) Rt = 3.34 min; m/z $[M+H]^+$ = 422; m/z $[M-H]^-$ = 420.
Example 237 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methyl-5-isoxazolyl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.01 min; m/z $[M+H]^+$ = 382; m/z $[M-H]^-$ = 380.
Example 238 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(4-morpholinyl)phenyl]methyl}-2,5-piperazinedione LCMS (A) Rt = 3.31 min; m/z $[M+H]^+$ = 462; m/z $[M-H]^-$ = 460.
Example 239 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1,5-dimethyl-1*H*-pyrazol-3-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 2.95 min; m/z $[M+H]^+$ = 395; m/z $[M+formate]^-$ = 439.
Example 240 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 2.33 min; m/z $[M+H]^+$ = 395; m/z $[M-H]^-$ = 393.
Example 241 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 2.97 min; m/z $[M+H]^+$ = 395; m/z $[M+formate]^-$ = 439.
Example 242 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(4-morpholinyl)phenyl]methyl}-2,5-piperazinedione LCMS (A) Rt = 3.32 min; m/z $[M+H]^+$ = 462.
Example 243) (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(2-oxo-1,2-dihydro-3-pyridinyl)methyl]-2,5-piperazinedione LCMS (A) Rt = 2.76 min; m/z $[M+H]^+$ = 394; m/z $[M-H]^-$ = 392.
Example 244 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[1-(4-methylphenyl)-1*H*-pyrazol-4-yl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione ^1H NMR ($CDCl_3$) δ 7.89 (s, 1H), 7.65

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(s, 1H), 7.52 (d, 2H), 7.26 – 7.13 (m, 5H), 6.93 (d, 1H), 5.08 (d, 1H), 4.02 – 3.90 (m, 3H), 3.10 (m, 3H), 2.95 – 2.75 (m, 2H), 2.38 (s, 3H), 2.0 (m, 1H), 1.90 – 1.60 (m, 3H), 1.02 (d, 3H), 0.97 (d, 3H).

Example 245 *N*-(3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-*N*-methylacetamide ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H), 7.39 (t, 1H), 7.25 – 7.07 (m, 6H), 5.32 (d, 1H), 4.06 (dd, 1H), 3.97 (d, 1H), 3.47 (s, 1H), 3.24 (s, 3H), 3.17 – 3.07 (m, 3H), 2.95 – 2.75 (m, 2H), 2.0 – 1.75 (m, 5H), 1.68 – 1.57 (m, 1H), 0.95 (d, 3H), 0.93 (d, 3H).

Example 246 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[5-(2-pyridinyl)-2-thienyl]methyl}-2,5-piperazinedione LCMS (A) Rt = 3.36 min; m/z $[M+H]^+$ = 460; m/z $[M+formate]^-$ = 504.

Example 247 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(1*S*)-1-(4-methyl-1,3-thiazol-2-yl)ethyl]-2,5-piperazinedione LCMS (A) Rt = 3.21 min; m/z $[M+H]^+$ = 412; m/z $[M+formate]^-$ = 456.

Example 248 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(5-methyl-3-phenyl-4-isoxazolyl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.34 min; m/z $[M+H]^+$ = 458; m/z $[M+formate]^-$ = 502.

Example 249 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 2.91 min; m/z $[M+H]^+$ = 395.

Example 250 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(1*H*-pyrazol-1-yl)phenyl]methyl}-2,5-piperazinedione LCMS (B) Rt = 0.83 min; m/z $[M+H]^+$ = 443.

Example 251 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-(3-isoxazolylmethyl)-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.00 min; m/z $[M+H]^+$ = 368; m/z $[M-H]^-$ = 366.

Example 252 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(5-methyl-2-pyrazinyl)methyl]-2,5-piperazinedione LCMS (A) Rt = 2.93 min; m/z $[M+H]^+$ = 393;

Example 253 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1-methyl-1*H*-benzimidazol-2-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 2.96 min; m/z $[M+H]^+$ = 431; m/z $[M-H]^-$ = 429.

Example 254 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-{[(1,1-dimethylethyl)oxy]methyl}phenyl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.61 min; m/z $[M+H]^+$ = 463.

Example 255 (3*R*,6*R*)-1-[(4-acetylphenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.30 min; m/z $[M+H]^+$ = 419; m/z $[M-H]^-$ = 417.

Example 256 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(2-phenyl-2*H*-1,2,3-triazol-4-yl)methyl]-2,5-piperazinedione LCMS (A) Rt = 3.53 min; m/z $[M+H]^+$ = 444.

Example 257 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-(phenylmethyl)-2,5-piperazinedione LCMS (A) Rt = 3.36 min; m/z $[M+H]^+$ = 377; m/z

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[M+formate]$^-$ = 421.

Example 258 (3*R*,6*R*)-1-[(4-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.52 min; m/z [M+H]$^+$ = 411.

Example 259 3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide LCMS (A) Rt = 2.96 min; m/z [M+H]$^+$ = 434. m/z [M-H]$^-$ = 432.

Example 260 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[3-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione LCMS (A) Rt = 3.03 min; m/z [M+H]$^+$ = 455; m/z [M-H]$^-$ = 453.

Example 261 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*,*N*-dimethylbenzenesulfonamide LCMS (A) Rt = 3.21 min; m/z [M+H]$^+$ = 484; m/z [M-H]$^-$ = 482.

Example 262 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione LCMS (B) Rt = 0.74 min; m/z [M+H]$^+$ = 490.

Example 263 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.01 min; m/z [M+H]$^+$ = 383; m/z [M-H]$^-$ = 381.

Example 264 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-({4-[(trifluoromethyl)sulfonyl]phenyl}methyl)-2,5-piperazinedione LCMS (A) Rt = 3.49 min; m/z [M+H]$^+$ = 509.

Example 265 (3*R*,6*R*)-1-{[2-chloro-4-(methylsulfonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.15 min; m/z [M+H]$^+$ = 489/491; m/z [M-H]$^-$ = 487/489.

Example 266 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione LCMS (A) Rt = 3.21 min; m/z [M+H]$^+$ = 457; m/z [M+formate]$^-$ = 501.

Example 267 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(4-{[ethyl(methyl)amino]methyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione LCMS (A) Rt = 2.59 min; m/z [M+H]$^+$ = 462; m/z [M+formate]$^-$ = 506.

Example 268 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1-pyrrolidinylmethyl)phenyl]methyl}-2,5-piperazinedione LCMS (A) Rt = 2.61 min; m/z [M+H]$^+$ = 474.

Example 269 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]methyl}-6-phenyl-2,5-piperazinedione ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1H), 7.60 (m, 2H), 7.49 (t, 1H), 7.33 (d, 1H), 7.25 – 7.15 (m, 4H), 5.48 (d, 1H), 4.71 (d, 1H), 4.07 (dd, 1H), 3.87 (d, 1H), 3.25 (s, 3H), 3.19 (dd, 1H), 3.12 (m, 2H), 2.98 – 2.81 (m, 2H).

Example 270 (3*R*,6*R*)-6-cyclohexyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione LCMS (A) Rt = 3.65 min; m/z [M+H]$^+$ = 417; m/z [M+formate]$^-$ = 461.

Example 271 (3*R*,6*R*)-6-cyclopropyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-

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methylphenyl)methyl]-2,5-piperazinedione LCMS (A) Rt = 3.24 min; m/z $[M+H]^+$ = 375; m/z $[M+formate]^-$ = 419.

Example 272 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-1-{[2-(1-piperazinylsulfonyl)phenyl]methyl}-2,5-piperazinedione hydrochloride LCMS (A) Rt = 3.79 min; m/z $[M+H]^+$ = 491; m/z $[M-H]^-$ = 489.

Example 273 1,1-dimethylethyl 3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate LCMS (A) Rt = 3.77 min; m/z $[M+H]^+$ = 491; m/z $[M-H]^-$ = 489.

Example 274 (3*S*,6*S*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione LCMS (A) Rt = 3.25 min; m/z $[M+H]^+$ = 469; m/z $[M-H]^-$ = 467.

Example 275 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(2-pyrazinylamino)phenyl]methyl}-2,5-piperazinedione LCMS (B) Rt = 0.78 min; m/z $[M+H]^+$ = 470.

Example 276 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(1*H*-1,2,3-triazol-1-yl)phenyl]methyl}-2,5-piperazinedione LCMS (B) Rt = 0.76 min; m/z $[M+H]^+$ = 444.

Example 277 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl}-2,5-piperazinedione LCMS (B) Rt = 0.75 min; m/z $[M+H]^+$ = 444.

Example 278 (3*R*,6*R*)-6-cyclopentyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[4-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione LCMS (B) Rt = 0.76 min; m/z $[M+H]^+$ = 502.

Example 279 *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-4-morpholinecarboxamide HPLC (D) Rt = 2.92 min; m/z $[M+H]^+$ = 519.

Example 280 (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl}-2,5-piperazinedione LCMS (B) Rt = 0.85 min; m/z $[M+H]^+$ = 444.

Example 281 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)benzamide LCMS (B) Rt = 0.69 min; m/z $[M+H]^+$ = 464.

Example 282 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-*N*-[2-(methyloxy)ethyl]benzamide LCMS (D) Rt = 2.62 min; m/z $[M+H]^+$ = 492.

Example 283 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)-*N*-methylbenzamide LCMS (D) Rt = 2.39 min; m/z $[M+H]^+$ = 478.

Example 284 *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-4-morpholinecarboxamide LCMS (B) Rt = 0.76 min; m/z $[M+H]^+$ = 505.

Example 285 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-

piperazinyl]methyl}-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide LCMS (D) Rt = 2.29 min; m/z $[M+H]^+$ = 505.

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Example 286: The preparation of this compound has been described as Intermediate 14: (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(hydroxymethyl)phenyl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione.

Example 287: The preparation of this compound has been described as Intermediate 15: 1,1-Dimethylethyl 3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate.

Example 288: The preparation of this compound has been described as Intermediate 45: (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-({2-[(1,1-dimethylethyl)thio]phenyl}methyl)-6-(1-methylethyl)-2,5-piperazinedione.

Example 289: The preparation of this compound has been described as Intermediate 52: 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-1,3-benzenedicarboxylic acid.

Example 290: The preparation of this compound has been described as Intermediate 53: 2-{[(3*R*,6*R*)-3-(2,3-Dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-5-(methylsulfonyl)benzoic acid.

Example 291: The preparation of this compound has been described as Intermediate 54: 1,1-dimethylethyl 4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate.

Assay Procedures

Assay 1) Determination of antagonist affinity at human Oxytocin-1 receptors using FLIPR

Cell Culture

Adherent Chinese Hamster Ovary (CHO) cells, stably expressing the recombinant human Oxytocin-1 (hOT) receptor, were maintained in culture in DMEM:F12 medium (Sigma, cat no D6421), supplemented with 10% heat inactivated foetal calf serum (Gibco/Invitrogen, cat. no.01000-147), 2mM L-glutamine (Gibco/Invitrogen, cat. no. 25030-024) and 0.2mg/ml G418 (Gibco/Invitrogen, cat no.10131-027). Cells were grown as monolayers under 95%:5% air:CO_2 at 37°C and passaged every 3-4 days using TrypLE™ Express (Gibco/Invitrogen, cat no. 12604-013).

Measurement of $[Ca^{2+}]_i$ using the FLIPR™

CHO-hOT cells were seeded into black walled clear-base 384-well plates (Nunc) at a density of 10,000 cells per well in culture medium as described above and maintained overnight (95%:5% air:CO_2 at 37°C). After removal of culture medium, cells were incubated for 1h at 37°C in Tyrode's medium (NaCl, 145mM; KCl, 2.5mM; HEPES, 10mM; Glucose, 10mM; $MgCl_2$, 1.2mM; $CaCl_2$, 1.5mM) containing probenacid

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(0.7mg/ml), the cytoplasmic calcium indicator, Fluo-4 (4uM; Teflabs, USA) and the quenching agent Brilliant Black (250uM; Molecular Devices, UK). Cells were then incubated for an additional 30min at 37°C with either buffer alone or buffer containing OT antagonist, before being placed into a FLIPR™ (Molecular Devices, UK) to monitor cell fluorescence (λ_{ex} = 488nm, λ_{EM} = 540nm) before and after the addition of a submaximal concentration of oxytocin (EC80).

Data Analysis

Functional responses using FLIPR were analysed using Activity Base Version 5.0.10.

Assay 2) Determination of estimated antagonist affinity at human Oxytocin-1 receptors using Fluorescence Polarisation

Cell Culture

Adherent Chinese Hamster Ovary (CHO) cells, stably expressing the recombinant human Oxytocin-1 (hOT) receptor, were maintained in culture in DMEM:F12 medium (Sigma, cat no D6421), supplemented with 10% foetal calf serum (Gibco/Invitrogen, cat. no.01000-147), 2mM L-glutamine(Gibco/Invitrogen, cat. no. 25030-024) and 0.5mg/ml G418 (Gibco/Invitrogen, cat no.10131-027). Cells were grown as monolayers under 95%:5% air:CO_2 at 37°C and passaged every 3-4 days using HBSS + 0.6mM EDTA.

Membrane preparation (GSK UK Gene Expression & Protein Biochemistry).

Membranes were prepared from cells cultured in 1800cm2 roller bottles. Harvested cells (HBSS + 0.6 mM EDTA) were centrifuged at 250g for 5 mins at 4°C. This was repeated after re-suspending the pellets in 200mls on HBSS + 0.6mM EDTA. All subsequent steps were performed at 4°C. The cells were homogenised for 2 x 15 secs in 200mls of 50mM HEPES + 10-4M leupeptin + 25ug/ml bacitracin + 1mM EDTA + 1mM PMSF + 2uM Pepstatin A, (the latter 2 reagents added as fresh x100 and x 500 stocks respectively in ethanol). The homogenate was plunged onto ice for 5 mins after the first burst and 10-40 mins after the final burst to dissipate the foam. The homogenate was then centrifuged at 500g for 20 mins and the supernatant centrifuged for 36 mins at 48,000g. The pellet was re-suspended in the same buffer as above but without PMSF and Pepstatin A. The material was then forced through a 0.6mm needle, made up to the required volume, (usually x4 the volume of the original cell pellet), aliquoted and stored frozen at –80 deg C.

Measurement of OT binding using Fluorescence Polarisation

Compounds were prepared as 1 in 4 serial dilutions in 100% DMSO. Diluted compound was added to black Greiner 384 microplate at 0.5µl/well. Bodipy Tamra labelled oxytocin (Perkin Elmer Life Sciences custom request CUS54801) was diluted in assay buffer (10mM HEPES, 10mM MgCl2, 0.125mg/ml bovine serum albumin: pH7.4 with KOH) and added to the microplate using to give a final assay concentration of 0.5nM @ 20µl/well,

followed by the addition of CHO-hOT membrane, diluted in assay buffer, 20µl/well, to give a final assay concentration of 2.5µg/well. The plates were protected from light and incubated at room temperature for 2 hours before being read on an LJL Analyst (Molecular Devices) using Excitation filter wave length 535/22, Emission filter: wave length 580/30.

Data Analysis

Fluorescence Polarisation units from both the parallel and perpendicular reads were used to calculate the Anisotropy & Total Intensity of the compounds. The anisotropy values under went normalisation conversion then fitted to the 4 parameter logistic equation. As the assay is providing an estimate of receptor affinity, functional pKi correction (Cheng Prusoff relationship) was applied, assuming the pKd of Bodipy Tamra to be 9.9 (4x ligand concentration added). All analysis was conducted using Activity Base version 5.0 (IDBS).

Activity and utility of the compounds of the invention

Examples 1-185 and 187-232 were found to have at least one of:
i) a pKi value of 6.9 or greater in Assay 1;
ii) a pKi value of 7.5 or greater in Assay 2.

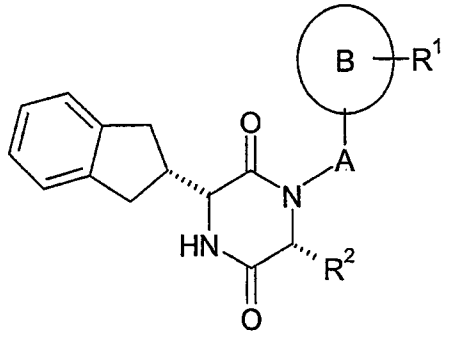
Examples 233-285 were found to have measurable activity in at least one of Assay 1 and Assay 2. Examples 233-285 may also have utility as Intermediates in the preparation of other compounds of Formula (I) or Formula (A).

Examples 186 and 286-291 were not tested in the Assays and have utility as Intermediates in the preparation of other compounds of Formula (I) or Formula (A).

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Claims

1. One or more chemical entities selected from a compound of Formula (I)



(I)

and physiologically acceptable derivatives thereof,

wherein:

A represents a C_{1-4}alkylene group optionally substituted by one or more C_{1-4}alkyl groups;

the ring B represents a mono-, bi- or tricyclic aryl or heteroaryl group containing one or more heteroatoms independently selected from O, S or N, wherein the aryl or heteroaryl group may be optionally substituted by one or more R^1 groups which may be independently selected from C_{1-6}cycloalkyl, C_{1-6}alkyl, C_{1-6}cycloalkoxy, C_{1-6}alkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, -Oheterocyclyl, -Oheteroaryl, $-S(O)_n$heterocyclyl or $-S(O)_n$heteroaryl (each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$); or R^1 may additionally be independently selected from halo, hydroxyl, $-NR^3R^4$, nitro, cyano, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, carboxyl, $-CONR^3R^4$, $-COR^5$, $-S(O)_nR^6$, $-NR^7COR^8$, $-S(O)_mNR^9R^{10}$ or $-NR^{11}S(O)_mR^{12}$;

R^2 represents C_{3-7}alkyl, C_{3-7} cycloalkyl or phenyl, each of which may be further optionally substituted by one or more groups selected from C_{1-4}alkyl or C_{3-7} cycloalkyl;

R^3 and R^4 independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be further optionally substituted by one or more groups independently selected from

halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-3}alkoxyC_{1-6}alkyl, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, COR^5, heteroaryl, heterocyclyl, aryl or -$NR^{3a}R^{4a}$;

or R^3 and R^4, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or a 4- to 7-membered heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$NR^{3a}R^{4a}$, COR^5, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, COR^5, heteroaryl, heterocyclyl, aryl or –$NR^{3a}R^{4a}$);

R^{3a} and R^{4a} independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocyclyl, or aryl;

or R^{3a} and R^{4a}, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or a 4- to 7-membered heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocyclyl, or aryl);

R^5 represents C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-6}alkyl, aryl, heteroaryl or heterocyclyl, wherein the C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-6}alkyl, aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, -$S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or -NR^3R^4;

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R^6 represents C_{1-6}alkyl, C_{1-6}cycloalkyl, trifluoroC_{1-6}alkyl, aryl, heteroaryl, or heterocyclyl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, trifluoroC_{1-6}alkyl, aryl, heteroaryl, or heterocyclyl groups may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-3}alkoxyC_{1-6}alkyl, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

R^7 represents H or C_{1-4}alkyl (optionally substituted by one or more groups independently selected from by halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$);

R_8 represents C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

or R^7 and R^8 together with the interconnecting atoms to which they are attached form a 4- to 7-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein the heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

R^9 and R^{10} independently represent H, C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl wherein the C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl group may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, , aryl, $-NR^3R^4$ or heterocyclyl optionally substituted with C_{1-6}alkyl;

or R^9 and R^{10}, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heteroaryl or a 4- to 7-membered heterocyclyl ring which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-NR^3R^4$, hydroxyl, aryl, heteroaryl or heterocyclyl (wherein the C_{1-4}alkyl, C_{1-4}alkoxy, aryl, heteroaryl or heterocyclyl groups on the 5- or 6-membered heteroaryl or 4- to 7-membered heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$);

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R^{11} represents H or C_{1-4}alkyl (optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$);

R^{12} represents C_{1-6}alkyl, C_{1-6}cycloalkyl, aryl, heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

or R^{11} and R^{12} together with the interconnecting atoms to which they are attached form a 4- to 7-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein the heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$;

n represents 0, 1 or 2;

and m represents 1 or 2.

2. At least one chemical entity comprising a compound Formula (IA) and physiologically acceptable derivatives, wherein the compound of Formula (IA) is a compound of Formula (I) as defined in claim 1 which is other than
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(2-pyridinyl)ethyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(4-nitrophenyl)ethyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(4-pyridinyl)ethyl]-2,5-piperazinedione
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-(4-pyridinylmethyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-1-yl)ethyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[6-(trifluoromethyl)-3-pyridinyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[2-(1-methyl-1*H*-imidazol-2-yl)ethyl]-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(3-pyridinyl)phenyl]-

methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[2-(1-methyl-1*H*-imidazol-5-yl)ethyl]-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{2-[4-(methylsulfonyl)phenyl]-ethyl}-2,5-piperazinedione;
N-(3-{2-[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]ethyl}phenyl)methanesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(2-methyl-2*H*-tetrazol-5-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1-ethyl-5-methyl-1*H*-pyrazol-4-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1-ethyl-1*H*-pyrazol-4-yl)methyl]-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({4-[(dimethylamino)methyl]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-{[3,5-bis(trifluoromethyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-6-cyclopropyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methylphenyl)methyl]-6-phenyl-2,5-piperazinedione; and
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]sulfinyl}phenyl)-methyl]-6-(1-ethylpropyl)-2,5-piperazinedione.

3. At least one chemical entity according to claim 1 or claim 2 wherein A represents CH_2, $CH(CH_3)$ or CH_2CH_2.

4. At least one chemical entity according to any preceding claim wherein the ring B represents phenyl, pyridyl, pyrimidinyl, quinolinyl or pyrazolyl.

5. At least one chemical entity according to any preceding claim wherein the one or more R^1 groups may be independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, (each of which may be optionally substituted by one or more groups independently selected from hydroxyl, C_{1-6}alkyl, C_{1-6}alkoxy, heterocyclyl, aryl or $-NR^3R^4$); or R^1 may additionally be independently selected from halo, hydroxyl, -

NR^3R^4, nitro, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, carboxyl, $-CONR^3R^4$, $-COR^5$, $-S(O)_nR^6$, $-NR^7COR^8$, $-S(O)_mNR^9R^{10}$ or $-NR^{11}S(O)_mR^{12}$.

6. At least one chemical entity according to any preceding claim wherein R^2 represents C_{3-5}alkyl, or R^2 represents C_{3-5}cycloalkyl which may be further optionally substituted by C_{1-2}alkyl, wherein the total number of carbon atoms in the R^2 group is between 3 and 5.

7. At least one chemical entity according to any preceding claim wherein R^3 and R^4 independently represent H or C_{1-4}alkyl which is optionally substituted by one or more groups independently selected from hydroxyl, C_{1-2}alkyl or $-NR^{3a}R^{4a}$, or R^3 and R^4, together with the interconnecting N-atom to which they are attached form a 5- or 6-membered heterocyclyl ring, which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5- or 6-membered heterocyclyl ring may be further optionally substituted by C_{1-4}alkyl.

8. At least one chemical entity according to any preceding claim wherein R^{3a} and R^{4a} independently represent C_{1-6}alkyl.

9. At least one chemical entity according to any preceding claim wherein R^5 represents C_{1-6}alkoxy which is optionally substituted with hydroxyl, C_{1-6}alkoxy, or $-NR^3R^4$.

10. At least one chemical entity according to any preceding claim wherein R^6 represents C_{1-6}alkyl, trifluoroC_{1-6}alkyl or heterocyclyl, each of which may be optionally substituted by one or more groups independently selected from C_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, heterocyclyl or $-NR^3R^4$.

11. At least one chemical entity according to any preceding claim wherein R^7 represents H or C_{1-4}alkyl.

12. At least one chemical entity according to any preceding claim wherein R_8 represents C_{1-6}alkyl or heterocyclyl or heteroaryl each of which may be optionally substituted by one or more groups independently selected from C_{1-6}alkyl, or $-NR^3R^4$.

13. At least one chemical entity according to any preceding claim wherein R^9 and R^{10} independently represent H, C_{1-6}alkyl, heterocyclyl or heteroaryl each of which is optionally substituted by one or more groups independently selected from hydroxyl, carboxyl, C_{1-6}alkyl, aryl $-NR^3R^4$ or heterocyclyl optionally substituted by C_{1-6}alkyl, or R^9 and R^{10}, together with the interconnecting N-atom to which they are attached form a

5-, 6- or 7-membered heterocyclyl ring which ring may additionally contain 1 or 2 heteroatoms independently selected from O, S or N; and wherein the 5-, 6- or 7-membered heterocyclyl ring may be further optionally substituted by one or more groups selected from C_{1-4}alkyl, or $-NR^3R^4$, (wherein the C_{1-4}alkyl group may be further optionally substituted by C_{1-6}alkoxy).

14. At least one chemical entity according to any preceding claim wherein R^{11} represents H or C_{1-4}alkyl.

15. At least one chemical entity according to any preceding claim wherein R^{12} represents C_{1-6}alkyl.

16. At least one chemical entity according to any preceding claim wherein R^{11} and R^{12} together with the interconnecting atoms to which they are attached form a 5- or 6-membered heterocyclyl ring which ring may additionally contain one or more heteroatoms independently selected from O, S or N, and wherein the heterocyclyl ring may be further optionally substituted by one or more groups independently selected from halo, hydroxyl, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoroC_{1-4}alkyl, trifluoroC_{1-4}alkoxy, $-S(O)_nR^6$, heteroaryl, heterocyclyl, aryl or $-NR^3R^4$.

17. At least one chemical entity according to any preceding claim wherein n represents 2.

18. At least one chemical entity according to any preceding claim wherein m represents 2.

19. At least one chemical entity according to any preceding claim selected from the group consisting of:
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2(hydroxymethyl)benzyl]-piperazine-2,5-dione;
methyl 2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzoate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(methyloxy)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-methylphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methyloxy)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methyloxy)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(trifluoromethyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-methylphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-[(3-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-fluorophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(1-piperidinylmethyl)-phenyl]methyl}-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[2-(dimethylamino)ethyl]oxy}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-fluorophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(3-fluorophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(trifluoromethyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(trifluoromethyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(trifluoromethyl)oxy]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({3-[(trifluoromethyl)oxy]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2,6-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2,6-dichlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-pyridinylmethyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2,2-dimethylpropyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1R)-1-phenylethyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2,6-dimethyl-3-pyridinyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;

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(3*R*,6*R*)-1-{[2,4-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-bromophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethyl-benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-hydroxyphenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(3-nitrophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(2-nitrophenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-({3-[(difluoromethyl)oxy]phenyl}methyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-[(3-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(3,4-dichlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-{[3,5-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(trifluoromethyl)oxy]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3,5-dimethylphenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(phenylmethyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(4-chlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[3-(2-pyridinyloxy)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;

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(3*R*,6*R*)-6-cyclohexyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylphenyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-6-(dicyclopropylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2,2-dimethylpropyl)-1-{[2-(methylsulfonyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(trifluoromethyl)-sulfonyl]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methyloxy)-4-(methylsulfonyl)phenyl]-methyl}-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methyloxy)-4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2-chloro-4-(methylsulfonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(1,1-dimethylethyl)thio]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(methylsulfonyl)-2-pyridinyl]methyl}-2,5-piperazinedione ;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(2-nitrobenzyl)piperazine-2,5-dione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-(1-methyl-4-piperidinyl)benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[4-(dimethylamino)-1-piperidinyl]-carbonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(1-methyl-4-piperidinyl)benzamide formate;

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2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[3-(dimethylamino)propyl]-*N*-methylbenzamide formate;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[3-(dimethylamino)propyl]benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methyl-1-piperazinyl)-carbonyl]phenyl}methyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(4-morpholinyl)ethyl]benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(2-hydroxyethyl)benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(2-hydroxyethyl)-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-4-piperidinylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1-piperazinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(dimethylamino)methyl]phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzenesulfonamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethyl-propyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethyl-benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-morpholinylsulfonyl)-phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzene-sulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methyl-1-piperazinyl)-sulfonyl]phenyl}-methyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(1-methyl-4-piperidinyl)-benzenesulfonamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethyl-propyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-(1-methyl-4-piperidinyl)benzenesulfonamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(4-morpholinyl)ethyl]benzene-sulfonamide;

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2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]-benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(4-ethyl-1-piperazinyl)sulfonyl]phenyl}-methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-({4-[2-(methyloxy)ethyl]-1-piperazinyl}sulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1-piperazinylsulfonyl)-phenyl]methyl}-2,5-piperazinedione hydrochloride;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylthio)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(4-piperidinylsulfonyl)-phenyl]methyl}-2,5-piperazinedione hydrochloride;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-({1-[2-(methyloxy)-ethyl]-4-piperidinyl}sulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-{[3-(4-morpholinyl)propyl]-thio}phenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-{[3-(4-morpholinyl)propyl]-sulfonyl}phenyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]thio}phenyl)-methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methyl-4-piperidinyl)-thio]phenyl}methyl)-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methyl-4-piperidinyl)-sulfonyl]phenyl}methyl)-2,5-piperazinedione formate;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({2-[(1-ethyl-4-piperidinyl)sulfonyl]phenyl}-methyl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-Aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)methanesulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)ethane-sulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-2-propanesulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-*N*-methylmethanesulfonamide ;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(1,1-dioxido-2-isothiazolidinyl)phenyl]-methyl}-6-(1-ethylpropyl)-2,5-piperazinedione;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)acetamide;
N^1-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-N^3,N^3-dimethyl-ß-alaninamide formate;

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N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-phenyl)-4-(dimethyl-amino)butanamide formate;
(formic acid - *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-1-methyl-4-piperidinecarboxamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(2-oxo-1-pyrrolidinyl)-phenyl]methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzenesulfonamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-{[ethyl(methyl)amino]methyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[1-(3-methylphenyl)-1*H*-pyrazol-4-yl]methyl}-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-[2-(3-pyridinyl)ethyl]-2,5-piperazinedione;
N-(3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)methanesulfonamide;
N-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)-*N*-methylacetamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{2-[4-(methyloxy)-3-(methylsulfonyl)phenyl]-ethyl}-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(1*S*)-1-phenylethyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(3-pyridinylmethyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-(4-pyridinylmethyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1,1-dimethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-oxo-1,2-dihydro-3-pyridinyl)methyl]-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(2-hydroxyphenyl)methyl]-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[1-(phenylmethyl)-1*H*-pyrazol-4-yl]methyl}-2,5-piperazinedione;

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(3*R*,6*R*)-6-cyclopentyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[2-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylthio)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylthio)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2,4-dichlorophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-(2-biphenylylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[2-(3-pyridinyl)ethyl]-2,5-piperazinedione;
(3*R*,6*R*)-6-(dicyclopropylmethyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(3-methylphenyl)-methyl]-2,5-piperazinedione;
(3*R*,6*R*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(4-{[2-(dimethylamino)ethyl]oxy}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(1-pyrrolidinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinylmethyl)-phenyl]methyl}-2,5-piperazinedione;
formic acid - (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({3-[(dimethylamino)methyl]-phenyl}methyl)-6-(1-ethylpropyl)-2,5-piperazinedione (1:1);
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-1-[(3-methylphenyl)methyl]-2,5-piperazinedione;
N-cyclopropyl-4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]methyl}benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[3-(3-pyridinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-fluoro-2-(hydroxymethyl)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(2-pyrazinylamino)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(2-pyrimidinylamino)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[4-(2-pyrimidinylamino)-phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(1-methyl-1*H*-imidazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({4-[(1-methyl-1*H*-imidazol-2-yl)amino]phenyl}-methyl)-6-(2-methylpropyl)-2,5-piperazinedione;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-({4-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({4-[(5-methyl-1,3-thiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-({4-[(5-methyl-1,3-thiazol-2-yl)amino]phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-pyrazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-1,2,3-triazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(1*H*-tetrazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1*H*-tetrazol-1-yl)phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-5-fluorobenzoic acid;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-5-fluoro-*N*,*N*-dimethylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-fluoro-2-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-5-fluoro-*N*-(2-hydroxyethyl)benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*-dimethylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzamide;
3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;

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3-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[3-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzoic acid;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}benzamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(4-morpholinylcarbonyl)-phenyl]methyl}-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-(2-hydroxyethyl)benzamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-[2-(methyloxy)ethyl]benzamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-[2-(dimethylamino)ethyl]-*N*-methylbenzamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)-*N*-methylbenzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-({4-[(4-methyl-1-piperazinyl)carbonyl]-phenyl}methyl)-6-(2-methylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-{1-[2-(methyloxy)ethyl]-4-piperidinyl}benzamide;
(3*R*,6*R*)-1-{[2,4-bis(hydroxymethyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylthio)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2,4-bis(1-pyrrolidinylcarbonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-{[2,4-bis(4-morpholinylcarbonyl)phenyl]methyl}-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*,*N*',*N*'-tetramethyl-1,3-benzenedicarboxamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*'-bis(2-hydroxyethyl)-*N*,*N*'-dimethyl-1,3-benzenedicarboxamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*'-bis[2-(dimethylamino)ethyl]-*N*,*N*'-dimethyl-1,3-benzenedicarboxamide;
4-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*,*N*'-dimethyl-*N*,*N*'-bis[2-(methyloxy)ethyl]-1,3-benzenedicarboxamide;
(3*R*,6*R*)-1-({2,4-bis[(4-methyl-1-piperazinyl)carbonyl]phenyl}methyl)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-piperazinedione;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(hydroxymethyl)-4-(methylsulfonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[4-(methylsulfonyl)-2-(4-morpholinylcarbonyl)phenyl]methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-[(4-methyl-1-piperazinyl)-carbonyl]-4-(methylsulfonyl) phenyl]methyl}-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-methyl-*N*-[2-(methyloxy)ethyl]-5-(methylsulfonyl)benzamide;
N-[2-(diethylamino)ethyl]-2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-methyl-5-(methylsulfonyl)benzamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-[(4-(methylsulfonyl)-2-{[(2*S*)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl}phenyl)methyl]-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}-*N*-(2-hydroxyethyl)benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(4-methylhexahydro-1*H*-1,4-diazepin-1-yl)sulfonyl]phenyl}methyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}-*N*-{[(2*R*)-1-ethyl-2-pyrrolidinyl]methyl}benzenesulfonamide;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[(3*S*)-3-(dimethylamino)-1-pyrrolidinyl]-sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[(3*R*)-3-(dimethylamino)-1-pyrrolidinyl]-sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-methylethyl)-2,5-dioxo-1-piperazinyl]-methyl}benzenesulfonamide;
N-[(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]-methyl}phenyl)sulfonyl]glycine;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-({2-[(1-methylethyl)sulfonyl]-phenyl}methyl)-2,5-piperazinedione;
(3*R*,6*R*)-1-[(2-aminophenyl)methyl]-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-2,5-piperazinedione;
formic acid - *N*-(2-{[(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-2,5-dioxo-1-piperazinyl]methyl}phenyl)-N^2,N^2-dimethylglycinamide (1:1);
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1*H*-imidazol-1-yl)phenyl]-methyl}-2,5-piperazinedione;
formic acid - (3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(2-{[3-(dimethylamino)propyl]-sulfonyl}phenyl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione (1:1);
(3*R*,6*R*)-6-cyclopentyl-3-(2,3-dihydro-1*H*-inden-2-yl)-1-{[4-(methylsulfonyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-1-[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]-6-(1-ethylpropyl)-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;

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(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(2-methylpropyl)-1-{[2-(methylsulfinyl)phenyl]-methyl}-2,5-piperazinedione;
(3*R*,6*R*)-3-(2,3-dihydro-1*H*-inden-2-yl)-6-(1-ethylpropyl)-1-{[2-(1*H*-pyrazol-1-yl)phenyl]-methyl}-2,5-piperazinedione;
and physiologically acceptable derivatives thereof.

20. A pharmaceutical composition comprising at least one chemical entity comprising a compound of Formula (IA) and physiologically acceptable derivatives thereof according to any one of claims 2 to 19 and a pharmaceutically acceptable carrier or diluent.

21. At least one chemical entity comprising a compound of Formula (IA) and physiologically acceptable derivatives thereof according to any one of claims 2 to 19 for use in therapy.

22. At least one chemical entity comprising a compound of Formula (IA) and physiologically acceptable derivatives thereof according to any one of claims 2 to 19 for use in the treatment or prevention of diseases or conditions mediated through the action of oxytocin.

23. Use of at least one chemical entity comprising a compound of Formula (IA) and physiologically acceptable derivatives thereof according to any one of claims 2 to 19 in the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

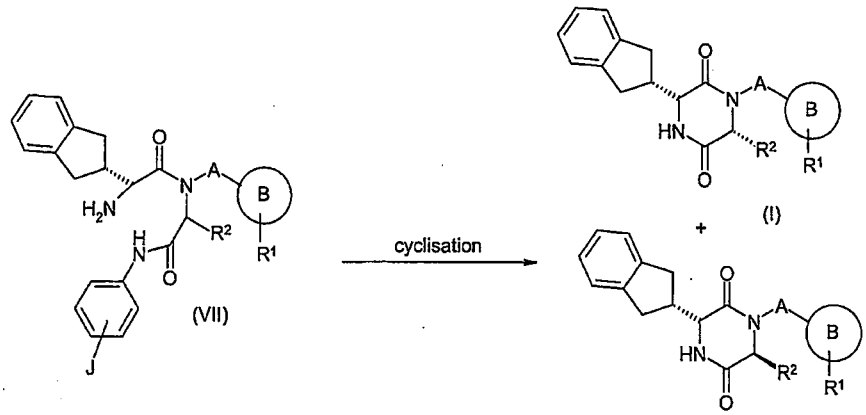
24. Use of at least one chemical entity comprising a compound of Formula (IA) and physiologically acceptable derivatives thereof according to any one of claims 2 to 19 in the manufacture of a medicament for the treatment of one or more diseases or conditions selected from pre-term labour, dysmenorrhea and endometriosis.

25. A method of treating or preventing diseases or conditions mediated through the action of oxytocin, which comprises administering to a mammal in need thereof an effective amount of at least one chemical entity comprising a compound of Formula (IA) and physiologically acceptable derivatives thereof according to any one of claims 2 to 19.

26. A method according to claim 25 wherein the disease or condition is selected from pre-term labour, dysmenorrhea and endometriosis.

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27. A process for the preparation of a compound of Formula (I) according to claim 1 comprising cyclisation of a compound of Formula (VII), wherein A, B, R^1 and R^2 are as defined for Formula (I), and J is an optional substituent, optionally in the presence of a suitable acid or base.



INTERNATIONAL SEARCH REPORT

International application No
.../GB2005/005007

154

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D241/08 A61P15/06

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)
C07D 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.
A	WO 03/053443 A (GLAXO GROUP LIMITED) 3 July 2003 (2003-07-03) cited in the application the whole document	1-27
P,A	WO 2005/000840 A (GLAXO GROUP LIMITED) 6 January 2005 (2005-01-06) cited in the application the whole document	1-27

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2006	03/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cortés, J

INTERNATIONAL SEARCH REPORT

ırnational application No.
PCT/GB2005/005007

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of 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
.../GB2005/005007

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03053443 A	03-07-2003	AU 2002364304 A1	09-07-2003
		BR 0215277 A	14-12-2004
		CA 2471355 A1	03-07-2003
		CN 1606443 A	13-04-2005
		EP 1458393 A1	22-09-2004
		HU 0500136 A2	30-05-2005
		JP 2005517663 T	16-06-2005
		MX PA04006033 A	27-09-2004
		US 2005148572 A1	07-07-2005
		ZA 200404326 A	26-07-2005
WO 2005000840 A	06-01-2005	AU 2004251868 A1	06-01-2005
		CA 2530310 A1	06-01-2005

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DERIVADOS DE (3R,6R) - 3- (2,3- DIHIDRO- 1H- INDEN- 2- IL) - 2,5- PIPERAZINADIONA 1,6 SUSTITUIDA COMO ANTAGONISTAS DE RECEPTORES DE OXTOCINA PARA EL TRATAMIENTO DE TRABAJO DE PARTO PRE- TÉRMINO, DISMENORREA Y ENDOMETRIOSIS

CAMPO DEL INVENTO

Este invento se relaciona con nuevos derivados de dicetopiperazina que tienen una acción antagonista potente y selectiva en el recetor de oxitocina, con procesos para su preparación, con composiciones farmacéuticas que los contienen y con su uso en medicina.

ANTECEDENTES DEL INVENTO

US5817751 describe métodos combinatoriales y de fase sólida para la síntesis de diversos derivados de dicetopiperazina y el uso de estos métodos para crear bibliotecas de diversos derivados de dicetopiperazina.

WO99/47549 describe derivados de dicetopiperazina incluyendo derivados de 3- bencil- 2,5- dicetopiperazina como inhibidores de la fructosa- 1,6- bisfosfato (FBPasa) .

WO99/38844 describe un método para preparar compuestos N- [alifáticos o aromáticos) carbonil]- 2- aminoacetamina y su ciclización para proporcionar entre otros, derivados de dicetopiperazina.

WO99/37304 describe compuestos oxaheterocíclilos incluyendo compuestos oxapiperazininilos que son inhibidores de Factor Xa.

WO03/053443 describe derivados de dicetopiperazina los cuales exhiben actividad como antagonistas selectivos en el receptor de oxitocina.

La hormona oxitocina es un potente contractor del útero y se utiliza para la inducción o magnificación del trabajo de parto. También la densidad de receptores de oxitocina uterina

aumenta significativamente más de 100 veces durante embarazo y picos en trabajo de parto (pre-término y a término) . 158

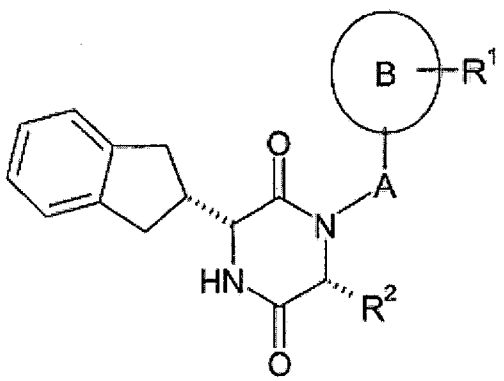
Nacimientos/trabajo de parto pre- término (entre 24 y 37 semanas) producen 60% aproximadamente de mortalidad/morbilidad infantil y por lo tanto se debe utilizar un compuesto que inhiba las acciones uterinas de oxitocina ej., antagonistas de oxitocina, para la prevención o control de trabajo de parto pre- término.

RESUMEN DEL INVENTO

Hemos encontrado una clase de derivados de dicetopiperazina que exhibe un nivel particularmente útil de actividad como antagonistas selectivos en el receptor de oxitocina.

DESCRIPCION DETALLADA DEL INVENTO

El presente invento proporciona al menos una entidad química, seleccionada de un compuesto de la Formula (I) :



(I)

y derivados fisiológicamente aceptables del mismo,

en donde:

A representa un grupo C1- 4alquileno opcionalmente sustituido por uno o más grupos C1-4alquilo;

El anillo B representa un grupo arilo o heteroarilo mono- , bi- o tricíclico que contiene uno o más heteroátomos independientemente seleccionados de O, S o N, en donde el grupo arilo o

heteroarilo se puede opcionalmente sustituir por uno o más grupos R^1 los cuales se pueden seleccionar independientemente de C1- 6cicloalquilo, C1- 6alquilo, C1- 6cicloalcoxilo, C1- 6alcoxilo, arilo, aralquilo, heterociclilo, heteroarilo, - Oheterociclilo, - Oheteroarilo, - S(O) nheterociclilo o –S(O) nheteroarilo (cada uno de los cuales se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4) ; o R1 se puede seleccionar independientemente de halo, hidroxilo, - NR3R4, nitro, ciano, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, carboxilo, - CONR3R4, - COR5, - S(O) nR6, - NR7COR8, - S(O) mNR9R10 o –NR11S(O) mR12;

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R^2 representa C3- 7alquilo, C3- 7cicloalquilo o fenilo, cada uno de los cuales se puede sustituir opcionalmente por uno o más grupos seleccionados de C1- 4alquilo o C3- 7cicloalquilo;

R^3 y R^4 independientemente representan H, C1- &alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir por uno o mas grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, C1- 3alcoxiC1- 6alquilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, COR^5, heteroarilo, heterociclilo, arilo o $–NR^3aR^4a$;

O R^3 y R^4, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un heteroarilo de 5 o 6 miembros o un anillo heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - $NR^{3a}R^{4a}$, COR^5, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alkoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, COR^5, heteroarilo, heterociclilo, arilo o $–NR^{3a}R^{4a}$) ;

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R^{3a} y R^{4a} independientemente representan H, C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, o arilo.

O R^{3a} y R^{4a}, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un heteroarilo de 5 o 6 miembros o un anillo heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alcoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente solucionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, o arilo) ;

R^5 representa C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 6alquilo, arilo, heteroarilo o heterociclilo, en donde los grupos C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 6alquilo, arilo, heteroarilo o heterociclilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4;

R^6 representa C1- 6alquilo, C1- 6cicloalquilo, trifluoroC1- 6alquilo, arilo, heteroarilo, o heterociclilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, trifluoroC1- 6alquilo, arilo, heteroarilo, o heterociclilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, c1- 6alquilo, C1- 6- alcoxilo, C1- 3alcoxiloc1- 6alquilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, heteroarilo, heterociclilo, arilo o $–NR^3R^4$;

R7 representa H o C1- 4alquilo (opcionalmente sustituido por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

R^8 representa C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo cada uno de los cuales se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

O R^7 y R^8 junto con los átomos de interconexión a los cuales están unidos forman un anillo de heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener uno o más heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo se puede opcionalmente sustituir por uno o más grupos seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $–NR^3R^4$;

R9 y R10 independientemente representan H, C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, arilo, NR^3R^4 o heterociclilo opcionalmente sustituido por C1- 6alquilo;

O R^9 y R^{10}, junto con el átomo de interconexión al cual están unidos forman un anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros, tal anillo adicionalmente puede contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - $NR^{3a}R^{4a}$, COR^5, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alkoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6

miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $-NR^{3a}R^{4a}$) ;

R^{11} representa H o C1- 4alquilo (opcionalmente sustituido por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

R^{12} representa C1- 6alquilo C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo, o heteroarilo cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

O R^{11} y R^{12} junto con los átomos de interconexión a los cuales están unidos forman un anillo heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $-NR^3R^4$;) ;

n representa 0, 1 o 2;

y m representa 1 o 2.

En un aspecto del invento se proporciona al menos una entidad química que comprende un compuesto de la Formula (IA) y derivados fisiológicamente aceptables de los mismos, en donde el compuesto de la formula (IA) es un compuesto de la Formula (I) el cual es diferente de un compuesto seleccionado de la Lista 1:

Lista 1

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (2- piridinil) etil]- 2,5- piperazinadiona; 163

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (4- nitrofenil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (4- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- (4- piridinilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (5,6,7,8- tetrahidroimidazo[1,5- a]piridin- 1- il) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[6- (trifluorometil) - 3- piridinil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [2- (1- metil- 1H- imidazol- 2- il) etil1- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (3- piridinil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [2- (1- metil- 1H- imidazol- 5- il) etil]- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (2- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {2- [4- (metilsulfonil) fenil]- etil}- 2,5- piperazinadiona;

N- (3- {2- [(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazina]etil}fenil) metanosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(1- metil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- metil- 2H- tetrazol- 5- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1- etil- 5- metil- 1H- pirazol- 4- il) - metil]- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1- etil- 1H- pirazol- 4- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[1- metil- 5- (trifluorometil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- metilamino) metil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

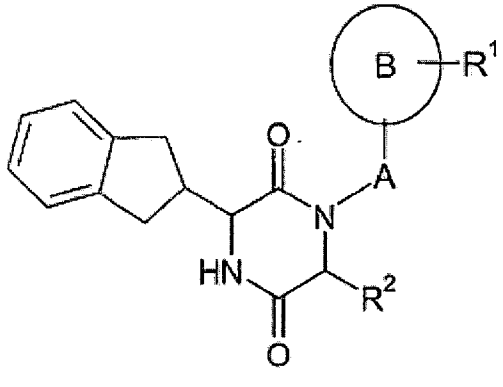
(3R, 6R) - 1- {[3,5- bis(trifluorometil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 6- ciclopropil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]- metil- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- metilfenil) metil]- 6- fenil- 2,5- piperazinadiona; y (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (2- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- dimetilamino) propil]sulfonil}fenil) - metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

En una realización alternativa del invento se proporciona al menos una entidad química seleccionada del compuesto de la Formula (A) :



(A)

y derivados, sales, solvatos y profármacos fisiológicamente aceptables de los mismos,

en donde:

A representa un grupo C1- 4alquileno opcionalmente sustituido por uno o más grupos C1- 4alquilo;

El anillo B representa un grupo arilo o heteroarilo mono- , bi- o tricíclico que contiene uno o más heteroátomos independientemente seleccionados de O, S o N, en donde el grupo arilo o heteroarilo se puede opcionalmente sustituir por uno o más grupos R^1 los cuales se pueden seleccionar independientemente de C1- 6cicloalquilo, C1- 6alquilo, C1- 6cicloalcoxilo, C1- 6alcoxilo, arilo, aralquilo, heterociclilo, heteroarilo, - Oheterociclilo, - Oheteroarilo, - S(O) nheterociclilo o –S(O) nheteroarilo (cada uno de los cuales se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4) ; o R1 se puede seleccionar independientemente de halo, hidroxilo, - NR3R4, nitro, ciano, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, carboxilo, - CONR3R4, - COR5, - S(O) nR6, - NR7COR8, - S(O) mNR9R10 o –NR11S(O) mR12;

R^2 representa C3- 7alquilo, C3- 7cicloalquilo o fenilo, cada uno de los cuales se puede sustituir opcionalmente por uno o más grupos seleccionados de C1- 4alquilo o C3- 7cicloalquilo;

R^3 y R^4 independientemente representan H, C1- &alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir por uno o mas grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, C1- 3alcoxiC1- 6alquilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, COR^5, heteroarilo, heterociclilo, arilo o $–NR^3aR^4a$;

o R^3 y R^4, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un heteroarilo de 5 o 6 miembros o un anillo heterociclilo de 4 a 7 miembros, tal anillo pueden

adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - $NR^{3a}R^{4a}$, COR^5, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alkoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, COR^5, heteroarilo, heterociclilo, arilo o $-NR^{3a}R^{4a}$) ;

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R3a y R4a independientemente representan H, C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, o arilo.

o R^{3a} y R^{4a}, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un heteroarilo de 5 o 6 miembros o un anillo heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alcoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente solucionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, o arilo) ;

R^5 representa C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 6alquilo, arilo, heteroarilo o heterociclilo, en donde los grupos C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 6alquilo, arilo, heteroarilo o heterociclilo se pueden opcionalmente sustituir por uno o más grupos independientemente

seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4;

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R^6 representa C1- 6alquilo, C1- 6cicloalquilo, trifluoroC1- 6alquilo, arilo, heteroarilo, o heterociclilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, trifluoroC1- 6alquilo, arilo, heteroarilo, o heterociclilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, c1- 6alquilo, C1- 6- alcoxilo, C1- 3alcoxiloC1- 6alquilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, heteroarilo, heterociclilo, arilo o $–NR^3R^4$;

R7 representa H o C1- 4alquilo (opcionalmente sustituido por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

R8 representa C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo cada uno de los cuales se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

O R^7 y R^8 junto con los átomos de interconexión a los cuales está unidos forman un anillo de heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener uno o más heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo se puede opcionalmente sustituir por uno o más grupos seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $–NR^3R^4$;

R^9 y R^{10} independientemente representan H, C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1-

4alcoxilo. –S(O) nR6, heteroarilo, arilo, NR^3R^4 o heterociclilo opcionalmente sustituido por C1-6alquilo;

O R^9 y R^{10}, junto con el átomo de interconexión al cual están unidos forman un anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros, tal anillo adicionalmente puede contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1-4alcoxilo, - $NR^{3a}R^{4a}$, COR^5, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1-4alquilo, C1- 4alkoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1-6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $–NR^{3a}R^{4a}$) ;

R^{11} representa H o C1- 4alquilo (opcionalmente sustituido por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

R^{12} representa C1- 6alquilo C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo, o heteroarilo cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

O R^{11} y R^{12} junto con los átomos de interconexión a los cuales están unidos forman un anillo heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $–NR^3R^4$;) ;

n representa 0, 1 o 2;

y m representa 1 o 2.

En un aspecto del invento se proporciona al menos una entidad química que comprende un compuesto de la Formula (A') y derivados fisiológicamente aceptables del mismo, en donde el compuesto de la formula (A') es un compuesto de la Formula (I) el cual es diferente de un compuesto seleccionado de la Lista 1 definida anteriormente.

Ciertos compuestos de la formula (I) o Formula (A) pueden existir en formas estereoisoméricas (ej., pueden contener uno o más átomos asimétricos de carbono) . Los estereoisómeros individuales (enantiómeros y diastereoisómeros) y mezclas de estos se incluyen dentro del alcance del presente invento. El presente invento también cubre los isómeros individuales de los compuestos representados por la Formula (I) o Formula (A) como mezclas con isómeros de los mismos en los cuales uno o más centros quirales son invertidos. Igualmente, se entiende que los compuestos de la Formula (I) o Formula (A) pueden existir en formas tautoméricas diferentes de aquella mostrada en la Formula y estas se incluyen dentro del alcance del presente invento.

Los compuestos de la Formula (I) o Formula (A) en donde al menos uno de los grupos R1 o R2 contiene un agrupamiento básico o ácido pueden formar sales con ácidos o bases fisiológicamente aceptables y referencia a compuestos de la Formula (I) o Formula (A) en la presente incluye tales sales.

Términos y Definiciones

Como se utiliza en la presente, los términos "derivado fisiológicamente aceptable" o "derivado farmacéuticamente aceptable", significan cualquier sal, solvato, o profármaco farmacéuticamente aceptable, ej., éster o carbamato, o sal o solvato de tal profármaco, de un compuesto de la Formula (I) o Formula (A) , el cual al administrar al receptor proporciona (directa o indirectamente) un compuesto de la Formula (I) o Formula (A) , o un metabolito activo o residuo del mismo. Los derivados farmacéuticamente aceptables son sales y solvatos.

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Como se utiliza en la presente, el término "profármaco" significa un compuesto el cual se convierte dentro del cuerpo, ej., mediante hidrólisis en la sangre, en su forma activa que tiene efectos medicinales. Profármacos farmacéuticamente aceptables se describen en T. Higuchi y V. Stella, Profármacos como Sistemas de Distribución Novedosos, Vol 14 de la Symposium A.C.S, y en Edgard B. Roche, ed., Vehiculos Bioreversibles en Diseño de Fármacos, Asociación Farmacéutica Americana y Pergamon Press, 1987, ambos incorporados en al presente como referencia. Los ésteres pueden ser activos por derecho propio y/o ser hidrolizables bajo condiciones *in vivo* en el cuerpo humano. Grupos ésteres apropiados hidrolizables *in vivo* farmacéuticamente aceptables incluyen aquellos que se descomponen con facilidad en el cuerpo humano para dejar el ácido precursor o su sal. Ejemplos de tales ésteres incluyen ésteres de alquilo y 1- (acetiloxi) etilo.

Como se utiliza en la presente, el término "alquilo" se refiere a cadenas de hidrocarburos lineales o ramificadas que contienen el número especificado de átomos de carbono. Por ejemplo, C1-6alquilo significa un alquilo lineal o ramificado que contiene al menos 1, y a la sumo 6 átomos de carbono. Ejemplos de "alquilo" como se utiliza en la presente incluyen, pero no están limitados a, metilo, etilo, n- propilo, n- butilo, n- pentilo, n- hexilo, isobutilo, isopropilo, t- butilo y 1,1-dimetilpropilo.

Como se utiliza en la presente, el término "alcoxilo" se refiere a un grupo alcoxilo lineal o ramificado que contiene el número especificado de átomos de carbono. Por ejemplo, C1-6alcoxilo significa un grupo alcoxilo lineal o ramificado que contiene al menos 1, y a lo sumo 6 átomos de carbono. Ejemplos de "alcoxilo" como se utiliza en la presente incluye, pero no está limitado a metoxilo, etoxilo, propoxilo, pro- 2- oxilo, butoxilo, but- 2- oxilo, 2- metilprop- 1-oxilo, 2- metilprop- 2- oxilo, pentoxilo o hexiloxilo.

Como se utiliza en la presente, el término "alquileno" como un grupo o parte de un grupo se refiere a un grupo enlazador de hidrocarburos saturados lineal o ramificado que contiene el número indicado de átomos de carbono. Ejemplos de tales grupos incluyen metileno, etileno y similares.

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Como se utiliza en la presente, el término "aralquilo" como un grupo o parte de un grupo se refiere a un grupo alquilo como se define en la presente el cual contiene el número indicado de átomos de carbono, el grupo alquilo es sustituido con un grupo arilo como se define en la presente.

Como se utiliza en la presente, el término "cicloalquilo" como un grupo o parte de un grupo se refiere a un grupo hidrocarburo cíclico saturado de 3 a 7 átomos de carbono. Ejemplos de tales grupos incluyen grupos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

Como se utiliza en la presente, el término "cicloalquiloxilo" como un grupo o parte de un grupo se refiere a un grupo O- cicloalquilo en donde cicloalquilo es como se definió en la presente.

Como se utiliza en la presente, el término "halógeno" o halo se refiere a fluor, cloro, bromo o yodo.

Como se utiliza en la presente, el término "arilo" se refiere a un compuesto cíclico compuesto de uno o más anillos de benceno e incluye fenilo, naftilo, fenantrenilo y antracenilo, cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $-NR^3R^4$.

Como se utiliza en la presente, el término "heteroarilo" como un grupo o parte de un grupo se refiere a un grupo aromático opcionalmente sustituido que comprende entre uno y cuatro heteroátomos seleccionados de N, O y S, el grupo aromático conteniendo uno, dos o tres anillos conjugados o fusionados de 5 o 6 miembros con al menos un anillo teniendo un sistema pi-electrónico conjugado. Los grupos heteroarilo se pueden sustituir mediante uno o más grupos independientemente seleccionados de halo, oxo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $-NR^3R^4$. Ejemplos de tales grupos heteroarilos de 5 miembros incluyen furanilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, pirazolilo, oxadiazolilo, tiadiazolilo,

triazolilo o tetrazolilo y estos heterociclos se pueden sustituir como se describió anteriormente. Ejemplos de grupos heteroarilos de 6- miembros de 6 miembros incluyen piridilo, piridazinilo, pirimidinilo, pirazinilo y triazinilo y estos heterociclos se pueden sustituir como se describió anteriormente. Ejemplos de grupos heteroarilo fusionados, incluyen bencimidazolilo, benzofuranilo, indolilo, indazolilo, benzoxazolilo, naftiridinilo, fterinilo y quinolinilo y estos grupos heteroarilo se pueden sustituir como se describió anteriormente.

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Como se utiliza en la presente, el término "heterociclilo" como un grupo o parte de un grupo se refiere a un grupo hidrocarburo cíclico parcialmente sustituido, de 3 a 7 miembros, saturado o parcialmente saturado que contiene entre uno y cuatro heteroátomos seleccionados de N, O y S. Los grupos heterociclilos se pueden sustituir por uno o más grupos independientemente seleccionados de halo, oxo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4. Ejemplos de grupos heterociclilos de 5 miembros incluyen pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, cada uno de los cuales se puede sustituir como se describió anteriormente. Ejemplos de grupos heterociclilos de 6 miembros incluyen piranilo, morfolino, tiomorfolino, piperidinilo, cada uno de estos se puede sustituir como se describió anteriormente. Un ejemplo de grupo heterociclilo de 7 miembros incliye homopiperazina (hexahidro- 1H- 1,4- diazepin- 1- ilo) . Además, el término "heterociclilo" incluye grupos heterociclicos fusionados, por ejemplo benzopiperidinilo, benzopiperazinilo, cada uno de estos se puede sustituir como se describió anteriormente.

Como se utiliza en la presente, el término "sustituido" se refiere a la sustitución con el sustituyente o sustituyentes nombrados, múltiples grados de sustitución se permiten a menos que se indique lo contrario.

Para evitar duda, el término "independientemente" significa que donde más de un sustituyente se selecciona a partir de un número de sustituyentes posibles, estos sustituyentes pueden ser iguales o diferentes.

Los compuestos del presente invento pueden estar en la forma de y/o se pueden administrar como una sal farmacéuticamente aceptable. Además, en ciertas realizaciones del invento, las sales farmacéuticamente aceptables de los compuestos según la Formula (I) o Formula (A) se pueden preferir sobre la base libre o ácido libre respectivos puesto que tales sales imparten mayor estabilidad o solubilidad a la molécula facilitando así la formulación en una forma de dosificación. Por consiguiente, el invento está dirigido adicionalmente a sales farmacéuticamente aceptables de los compuestos según la Formula (I) o Formula (A) .

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Como se utiliza en la presente, el término "sales farmacéuticamente aceptables" se refiere a sales que retienen la actividad biológica deseada del compuesto en cuestión y exhiben efectos toxicológicos indeseados mínimos. Para una reseña sobre sales apropiadas ver Berge, J.Pharm. Sci, 1977, 66, 1- 19. El término "sales farmacéuticamente aceptables" incluye tanto sales de adición ácida farmacéuticamente aceptables como sales de adición básica farmacéuticamente aceptables. Estas sales farmacéuticamente aceptables se pueden preparar *in situ* durante el aislamiento y purificación final del compuesto, o al reaccionar de manera separada el compuesto purificado en su forma ácida libre o básica libre con una base o ácido apropiado, respectivamente. La sal se puede precipitar a partir de la solución y se puede recolectar mediante filtración o se puede recubrir mediante evaporación del solvente.

Una sal de adición ácida se puede formar mediante reacción de un compuesto de la formula (I) con un ácido inorgánico u orgánico apropiado (tal como hidrobrómico, clorhidrico, sulfúrico, salfámico, nítrico, fosfórico, succinico, maleico, hidroximaleico, acrílico, fórmico, acético, hidroxiacético, fenilacético, butírico, isobutírico, propiónico, fumárico, cítrico, tartárico, láctico, mandélico, benzóico, o- acetoxibenzóico, clorobenzóico, metilbenzóico, dinitribenzóico, hidroxibenzóico, metoxibenzóico, salicílico, glutámico, esteárico, ascórbico, palmítico, oléico, piruvínico, pamoico, masónico, laurico, glutámico, aspártico, p- toluensulfónico, bencenosulfónico, metanosulfónico, etanosulfónico, 2- hidroxietanosulfónico, naftalensulfónico (ej., 2- naftalensulfónico) , p- aminobencenosulfónico (es decir, sulfanílico) , hexanóico, heptanóico, ftálico) , opcionalmente en un solvente apropiado tal como un solvente orgánico, para proporcionar la sal que usualmente es aislada por ejemplo mediante cristalización o filtración. Una sal de adición ácida farmacéuticamente aceptable de un compuesto de la formula

(I) puede comprender o ser por ejemplo una sal de hidrobromuro, hidrocloruro, hidroyoduro, sulfato, bisulfato, nitrato, fosfato, hidrogenfosfato, succinato, maleato, malato, formato, acetato, trifluoroacetato, sacarato, propionato, fumarato, citrato, tartrato, lactato, benzoato, salicitalto, glutamato, aspartato, p- toluensulfonato, bencenosulfonato, metanosulfonato, etanosulfonato, naftalensulfonato (ej., 2- naftalensulfonato) , metanosulfónica, etanosulfónica, p- toluensulfónica, isetionato o hexanoato. En una realización se proporciona las sales de formato e hidrocloruro de los compuestos del invento.

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Una sal de adición básica farmacéuticamente aceptable se puede formar mediante reacción de un compuesto de la formula (I) con una base orgánica o inorgánica apropiada (ej., amoniaco, trietilamina, etanolamina, trietanolamina, colina, arginina, lisina o histidina) , la cual usualmente es aislada por ejemplo mediante cristalización y filtración. Las sales básicas farmacéuticamente aceptables incluyen sales de amonio y sales con bases orgánicas, incluyendo sales de aminas primarias, secundarias y terciarias, incluyendo aminas alifáticas, aminas aromáticas, diaminas alifáticas, y hidroxialquilaminas, tales como metilamina, etilamina, isopropilamina, dietilamina, etilendiamina, etanolamina, trimetilamina, amina de diciclohexilo, dietanolamina, ciclohexilamina y N- metil- D- glucamina. Otras sales básicas farmacéuticamente apropiadas incluyen sales metálicas farmacéuticamente apropiadas, por ejemplo sales de metales alcalinos o metales alcalinoterreos farmacéuticamente aceptables tales como hidroxidos, carbonatos y bicarbonatos de sodio, potasio, litio, calcio, magnesio, aluminio, y zinc; en particular sales metálicas farmacéuticamente aceptables de una o mas fracciones ácidas carboxílicas que pueden estar presentes en el compuesto de la Formula (I) o formula (A) .

Se pueden utilizar otras sales no farmacéuticamente aceptables, por ejemplo oxalatos, por ejemplo en la separación de compuestos del invento, y se incluyen dentro del alcance de este invento.

El invento incluye dentro de su alcance todas las formas estoiquiométricas y no estoiquiométricas posibles de las sales de los compuestos de la Formula (I) .

Como se utiliza en la presente, el término "solvato" se refiere a un complejo de estoiquiometria variable formado mediante un soluto (en este invento, un compuesto de la Formula (I) o Formula (A) o una sal del mismo) y un solvente. Tales solventes para el propósito del invento pueden no interferir con la actividad biológica del soluto. Ejemplos de solventes apropiados incluyen agua, etanol y ácido acético. Más preferiblemente el solvente utilizado es agua y el solvato también se puede conocer como hidrato.

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En un aspecto del invento A representa CH2, CH(CH3) o CH2CH2. En otro aspecto, A representa CH2 o CH(CH3) . En un aspecto adicional, A representa CH2.

En un aspecto del invento el anillo B represent fenilo, piridilo, pirimidinilo, quinolinilo o pirazolilo. En otro aspecto el anillo B representa fenilo, piridilo, pirimidinilo o pirazolilo. En un aspecto adicional, el anillo B representa fenilo.

En un aspecto, el anillo B opcionalmente es sustiuido por uno o dos grupos R1. En otro aspecto, los grupos R1 se pueden seleccionar independientemente de C1- 6alquilo, C1- 6alcoxilo, arilo, aralquilo, heterociclilo, heteroarilo (cada uno de estos se puede sustituir opcionalmente por uno o más grupos independientemente seleccionados de hidroxilo, C1- 6alquilo, C1- 6alcoxilo, heterociclilo, arilo o –NR3R4) ; o R1 se puede adicionalmente independientemente seleccionar de halo, hidroxilo, - NR3R4; nitro, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, carboxilo, - $CONR^3R^4$, - COR5, - S(O) nR^6, - NR^7COR^8, - S(O) mNR^9R^{10} o- $NR^{11}S(O)\ mR^{12}$. En otro aspecto, los grupos R1 se pueden independientemente seleccionar de C1- 6alquilo, heteroarilo, por ejemplo pirazolilo, (cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de C1- 6alcoxilo o $–NR^3R^4$) ; o R^1 se puede adicionalmente independientemente seleccionar de $–NR^3R^4$, - $CONR^3R^4$, - S(O) nR^6, - NR^7COR^8 o – S(O) mNR^9R^{10}.

En un aspecto del invento R2 representa C3- 5alquilo, o R2 representa C3- 5cicloalquilo el cual se puede además opcionalmente sustituir por C1- 2alquilo, en donde el número total de átomos de carbono en el grupo R2 está entre 3 y 5.

En un aspecto del invento R3 y R4 independientemente representan H, C1- 6alquilo, C1- 6cicloalquilo, heterociclilo o heteroarilo en donde los gruoos C1- 6alquilo, C1- 6cicloalquilo, heterociclilo o heteroarilo se pueden adicionalmente opcionalmente sustituir por uno o mas grupos independientemente seleccionados de hidroxilo, c1- 6alquilo, C1- 6alcoxilo, c1- 3alcoxiC1- 6alquilo, heterociclilo, arilo o –NR3aR4a; o R3 y R4, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un anillo heterociclilo de 5 o 6 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N (por ejemplo morfolino o piperazina) ; y en donde el anillo heterociclilo de 5 o 6 miembros se puede opcionalmente sustituir por C1- 4 alquilo, (en donde el grupo C1- 4alquilo se puede opcionalmente sustituir por uno o mas grupos independientemente seleccionados de heterociclilo o arilo) . En otro aspecto R^3 y R^4 independientemente representan H o C1- 4alquilo el cual opcionalmente se sustituye por uno o más grupos independientemente seleccionados de hidroxilo, C1- 2alquilo o –NR3aR4a, o R^3 y R^4, junto con el átomo de interconexión al cual están unidos forman un anillo heterociclilo de 5 o 6 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N (por ejemplo morfolina o piperazina) ; y en donde el anillo heterociclilo de 5 o 6 miembros se puede opcionalmente sustituir por C1- 4alquilo.

En un aspecto del invento R3a y R4a independientemente presentan H o C1- 6alquilo. En otro aspecto R3a y R4a independientemente representan C1- 6alquilo.

En un aspecto del invento R5 representa C1- 6alcoxilo el cual opcionalmente se sustituye con hidroxilo, C1- 6alcoxilo, o $–NR^3R^4$ (por ejemplo NMe2, morfolina, piperidina, piperazina o pirrolidina) . En otro aspecto R5 representa C1- 3alcoxilo.

En un aspecto del invento R6 representa C1- 6alquilo, trifluoroC1- 6alquilo o heterociclilo, cada uno de estos opcionalmente se puede sustituir por uno o más grupos independientemente seleccionados de C1- 6alquilo, C1- 3alcoxiC1- 6alquilo, heterociclilo o –NR3R4 (por ejemplo NMe2, morfolina, piperidina o piperazina) . En otro aspecto R6 representa C1- 3alquilo.

En un aspecto del invento R^7 representa H o C1- 4alquilo.

En un aspecto del invento R^8 representa C1- 6alquilo o heterociclilo o heteroarilo cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de C1- 6alquilo, o $-NR^3R^4$.

En un aspecto del invento R^9 y R^{10} representan independientemente H, C1- 6alquilo, heterociclilo o heteroarilo cada uno de estos es opcionalmente sustituido por uno o mas grupos independientemente seleccionados de hidroxilo, carboxilo, C1- 6alquilo, arilo, - NR^3R^4 o heterociclilo opcionalmente sustituido por C1- 6alquilo, o R9 y R10, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un anillo heterociclico de 5, 6 o 7 miembros, tal anillo adicionalmente puede contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N (por ejemplo morfolina, piperidina o piperazina) ; y en donde el anillo heterociclilo puede además opcionalmente ser sustituido por uno o más grupos seleccionados de C1- 4alquilo, o $-NR^3R^4$, (en donde el grupo C1- 4alquilo se puede opcionalmente además sustituir por c1- 6alcoxilo) . En otro aspecto R^9 y R^{10} ambos representan CH3, o R^9 y R^{10}, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un anillo de morfolina, piperidina, piperazina o pirrolidina.

En un aspecto del invento R^{11} representa H o C1- 4alquilo. En otro aspecto del invento R^{12} representa C1- 6alquilo. En un aspecto adicional R^{11} y R^{12} junto con los átomos de interconexión al cual están unidos forman un anillo heterociclilo de 5 o 6 miembros, tal anillo puede adicionalmente contener uno o más heteroátomos independientemente seleccionados de O, S o N, y en donde el anillo heterociclilo puede opcionalmente además ser sustituido por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o $-NR^3R^4$.

En un aspecto del invento n representa 2.

En un aspecto del invento m representa 2.

En un aspecto del invento, para los compuestos de la Formula (A) , la estereoquímica de los dos centros quirales sobre el anillo central de piperazina- 2,5- diona es (3R, 6R) .

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Se debe entender que el presente invento cubre todas las combinaciones de aspectos del invento, incluyendo grupos apropiados, convenientes y preferidos descritos anteriormente.

En un aspecto, las entidades químicas útiles en el presente invento se pueden elegir de al menos una entidad química de la Formula (I) seleccionada del grupo que consta de:

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 1- [2- (hidroximetil) bencil]- piperazina- 2,5- diona;

metil 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (metiloxi) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metiloxi) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiloxi) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (trifluorimetil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 1- [(3- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- fluorofenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 1- (2- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 1- {[3- (1- piperidinilmetil) - fenil]metil}- 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[2- (dimetilamino) etil]oxi}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- fluorofenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(3- fluorofenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- fluorometil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluorometil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- fluorometil) oxi]- fenil}- metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({3- [trifluorometil) oxi]- fenil}- metil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,6- bis(metiloxi) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,6- diclorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- piridinilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2,2- dimetilpropil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1R) - 1- feniletil]- 2,5- piperazinadiona;

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(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2,6- dimetil- 3- piridinil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,4- bis(metiloxi) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(2- bromofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetil- bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- hidroxifenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(3- nitrofenil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- nitrofenil) metil- 2,5- piperazinadiona;

(3R, 6R) - 1- ({3- difluorometil) oxi]fenil}metil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (1,2,3- tiadiazol- 4- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 1- [3- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(3,4- diclorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 1- {[2- (4- morfolin) fenil]- metil}- 2,5- piperazinadiona;

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(3R, 6R) - 1- {[3,5- bis(metiloxi) fenil]- metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(trifluorometil) oxi]- fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3,5- dimetilfenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (fenilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(4- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[3- (2- piridiniloxi) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 6- ciclohexil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilfenil) - 1- {[2- (metilsulfonil) fenil]- metil}-

2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 1- {[2- (metilsulfonil) fenil]- metil}-

2,5- piperazinadiona;

(3R, 6R) - 6- (diciclopropilmetil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2,2- dimetilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(trifluorometil) - sulfonil]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metiloxi) - 4- (metilsulfonil) fenil]- metil}- 6- (2- metilpropil) - 2,5- piperazinadiona;

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(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiloxi) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- {[2- cloro- 4- (metilsulfonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(5- metil- 1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- (1,1- dimetil) tio]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- metil- 5- (trifluorometil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (metilsulfonil) - 2- piridinil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- nitrobencil) piperazina- 2,5- diona;

ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil}benzoico;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil}benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- (1- metil- 4- piperidinil) benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2{[4- (dimetilamino) - 1- piperidinil]- carbonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (1- metil- 4- piperidinil) benzamida formato;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (dimetilamino) etil]- N- metilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [3- (dimetilamino) propil]- N- metilbenzamida formato;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [3- (dimetilamino) propil]- N- metilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (dimetilamino) etil]benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(4- metil- 1- piperazinil) - carbonil]fenil}metil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (4- morfolinil) etil]benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (2- hidroxietil) benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (2- hidroxietil) - N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- 4- piperidinilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperazinilcarbonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- dimetilamino) metil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbencenosulfonamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetil- bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

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2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benceno- sulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- metil- 1- piperazinil) - sulfonil]fenil}- metil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (1- metil- 4- piperidinil) - bencenosulfonamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- (1- metil- 4- piperidinil) - bencenosulfonamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (4- morfolin) etil]benceno- sulfonamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (dimetilamino) etil]bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(4- etil- 1- piperazinil) sulfonil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- ({4- [2- (metiloxi) etil]- 1- piperazinil}sulfonil) fenil]metil}- 2,5- piperazinadiona;

hidrocloruro de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperazinilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperidiniltio) - fenil]metil}- 2,5- piperazinadiona;

hidrocloruro de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- piperazinilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- ({1- [2- (metiloxi) - etil]- 4- piperidinil}sulfonil) metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- {[3- (4- morfolinil) propil]- tio}fenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- {[3- (4- morfolin) propil]- sulfonil}fenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- (dimetilamino) propil]tio}fenil) metil]—6- (1- etilpropil) - 2,5- piperazinadiona;

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(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metil- 4- piperidinil) - tio]fenil}metil) - 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metil- 4- piperidinil) - sulfonil]fenil}metil) - 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(1- etil- 4- piperidinil) - sulfonil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona formato;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) metanosulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) etano- sulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - 2- propanosulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - N- metilmetanosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (1,1- dioxido- 2- isotiazolidinil) fenil]metil}- 6- (1- etilpropil) - 2,5- piperazinadiona;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) acetamida;

N^1- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - N^3, N^3- dimetil- β- alaninamida formato;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - 4- (dimetil- amino) butanamida formato;

(ácido formico - N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - 1- metil- 4- piperadinacarboxamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (2- oxo- 1- pirrolidin) - fenil]metil}- 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil- 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbencenosulfonamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil- 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[etil(metil) amino]metil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[1- (3metilfenil) - 1H- pirazolo- 4- il]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2(3- piridinil) etil]- 2,5- piperazinadiona;

N- (3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- .metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) metanosulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - N- metilacetamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {2- [4- (metiloxi) - 3- (metilsulfonamida) fenil]- etil}- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- metil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1S) - 1- feniletil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (3- piridinilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (4- piridinilmetil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1,1- dimetilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- oxo- 1,2- dihidro- 3- piridinil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- hidroxifenil) metil]- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[1- (fenilmetil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- [(2,4- diclorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- (2- bifenililmetil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [2- (3- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 1- {[3,4- bis(metiloxi) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(4- {[2- (dimetilamino) etil]oxi}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (1- pirrolidinilmetil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona;

ácido formico - (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({3- [(dimetilamino) metil]- fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona (1:1) ;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona;

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N- ciclopropil- 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metilpropil) - 1- {[3- (3- piridinil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluoro- 2- (hidroximetil) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (2- pirazinilamino) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (2- pirimidinilamino) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (2- pirimidinilamino) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(1- metil- 1H- imidazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- [(1- metil- 1H- imidazol- 2- il) amino]fenil}metil) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(5- metil- 1,3,4- tiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- ({4- [(5- metil- 1,3,4- tiadiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(5- metil- 1,3,- tiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- ({4- [(5- metil- 1,3,- tiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {4[- (1H- pirazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1H- 1,2,3- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1H- 1,2,4- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (2H- 1,2,3- triazol- 2- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (1H- tetrazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- tetrazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluorobenzoico;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluoro- N,N- dimetilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluoro- 2- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluoro- N- (2- hidroxietil) benzamida;

ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]benzoico;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

ácido 3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico;

3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

ácido 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) benzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metil- N- [2- (metiloxi) etil]benzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (dimetilamino) etil]- N- metilbenzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) - N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- [(4- metil- 1- piperazinil) carbonil]- fenil}metil) - 6- (2- metilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- {1- [2- (metiloxi) etil]- 4- piperadinil}benzamida;

(3R, 6R) - 1- {[2,4- bis(hidroximetil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metiltio) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,4- bis(1- pirrolidincarbonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

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(3R, 6R) - 1- {[2,4- bis(4- morfolinilcarbonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N,N`,N`- tetrametil- 1,3- bencenodicarboxamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- bis(2- hidroxietil) - N,N´- dimetil- 1,3- bencenodicarboxamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- bis[2- (dimetilamino) etil]- N,N´- dimetil- 1,3- bencenodicarboxamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- dimetil- N,N´- bis[2- (metiloxi) etil]- 1,3- bencenodicarboxamida;

(3R, 6R) - 1- {[2,4- bis(4- metil- 1- piperazinil) carbonil]fenil}]metil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) - 2- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- [(4- metil- 1- piperazinil) - carbonil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- [2- (metiloxi) etil]- 5- (metilsulfonil) benzamida;

N- [2- (dietilamino) etil]- 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- 5- (metilsulfonil) benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- metilsulfonil) - 2- {[(2S) - 2- (1- pirrolidinilmetil) - 1- pirrolidinil]carbonil}fenil) metil]- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (2- hidroxietil) bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(4- metilhexahidro- 1H- 1,4- diazepin- 1- il) sulfonil]fenil}metil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- {[(2R) - 1- etil- 2- pirrolidin]metil}bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[(3S) - 3- (dimetilamino) - 1- pirrolidinil]-sulfonil}fenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[(3R) - 3- (dimetilamino) - 1- pirrolidinil]-sulfonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 2,5- dioxo- 1- piperazinil]-metil}bencenosulfonamida;

N- [(2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) sulfonil]glicina.

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metiletil) sulfonil]-fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(2- aminofenil) metil- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5-piperazinadiona;

ácido formico - N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5-dioxo- 1- piperazinil]- metil}fenil) - N^2, N^2- dimetilglicinanida (1:1) ;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- imidazol- i1) fenil]-metil}- 2,5- piperazinadiona;

ácido formico - (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- dimetilamino) propil]-sulfonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona (1:1) ;

(3R, 6R) - 6- ciclopentil- 3- (2,3- dihidro- 1H- inden- 1- {[4- (metilsulfonil) fenil]- metil}- 2,5-piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[(1,5- dimetil- 1H- pirazol- 4- i1) - metil]- 6-(1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]-metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]-metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metilsulfonil) fenil]-metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metilsulfonil) fenil]-metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- pirazol- 1- il) fenil]- metil}- 2,5- piperazinadiona;
Y derivados fisiológicamente aceptables de los mismos.

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La capacidad de los compuestos de la Formula (I) o Formula (A) para inhibir las acciones de oxitocina se pueden determinar utilizando una variedad de procedimientos convencionales.

Por lo tanto, los compuestos de la Formula (I) o Formula (A) tienen una alta afinidad para los receptores de oxitocina sobre el útero de ratas y humanos y esto se puede determinar utilizando un procedimiento convencional. Por ejemplo la afinidad para los receptores de oxitocina sobre el útero de ratas se puede determinar mediante el procedimiento de Pettibone, Investigación de Desarrollo de Fármacos, 1993 (30) pp129- 142. Los compuestos del invento también exhiben alta afinidad en el receptor de oxitocina recombinante humano en células CHO y esto se puede demostrar de manera conveniente utilizando el procedimiento descrito por Wyatt Biorganic & Medicinal Chemistry Letters, 2001 (11) pp1301- 1305.

Por lo tanto los compuestos del invento son útiles en el tratamiento o prevención de enfermedades y/o condiciones mediadas a través de la acción de oxitocina. Ejemplos de tales enfermedades y/o condiciones incluyen trabajo de parto pre- término, dismenorrea, endometriosis e hiperplasia prostática benigna.

Los compuestos también pueden ser útiles para retardar el trabajo de parto antes de cesárea electiva o remisión del paciente a otro centro de atención, tratamiento de disfunción sexual (masculino y femenino) , particularmente eyaculación precoz, obesidad, trastornos alimenticios, falla cardiaca congestiva, hipertensión arterial, cirrosis hepática, hipertensión nefrítica u ocular, trastorno obsesivo compulsivo y trastornos neuropsiquiatricos. Los compuestos del invento también pueden ser útiles para mejorar tasas de fertilidad en animales, ej., animales domésticos.

Por lo tanto, el invento sustenta el uso de al menos una entidad química que comprende un compuesto de la Formula (IA) o Formula (A') y derivados fisiológicamente aceptables del mismo para el uso en terapia y en particular el uso como medicina para antagonizar los efectos de

oxitocina sobre el receptor de oxitocina y para el uso en el tratamiento o prevención de enfermedades o condiciones mediadas por la acción de oxitocina.

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El invento también sustenta el uso de al menos una entidad química que comprende un compuesto de la Formula (IA) o Formula (A') y derivados fisiológicamente aceptables del mismo en la fabricación de un medicamento par antagonizar los efectos de oxitocina sobre el receptor de oxitocina. En una realización, el invento sustenta el uso de al menos una entidad química que comprende un compuesto de la Formula (IA) o Formula (A') y derivados fisiológicamente aceptables del mismo en la fabricación de un medicamento para el tratamiento de una o más enfermedades o condiciones seleccionadas de trabajo de parto pre- término, dismenorrea y endometriosis.

Según un aspecto adicional, el invento también sustenta un método para antagonizar los efectos de oxitocina sobre el receptor de oxitocina, comprendiendo administrar a un paciente, una cantidad antagonística de al menos una entidad química que comprende al menos una entidad química que comprende un compuesto de la Formula (IA) o formula (A') y derivados fisiológicamente aceptables del mismo.

Según otro aspecto, el invento también sustenta un método de tratamiento o prevención de enfermedades o condiciones mediadas a través de la acción de oxitocina, el cual comprende la administración a un mamífero en necesidad del mismo de una cantidad efectiva de al menos una entidad química que comprende un compuesto de la Formula (IA) o Formula (A') y derivados fisiológicamente aceptables del mismo. En un aspecto, la enfermedad o condición se selecciona entre trabajo de parto pre- término, dismenorrea y endometriosis.

Se apreciará por aquellos con experiencia en el estado de la técnica que la referencia en la presente a tratamiento se extiende a la profilactica así como también al tratamiento de enfermedades establecidas o síntomas.

Además se apreciará que la cantidad de un compuesto del invento requerido para utilizar en el tratamiento variará con la naturaleza de la condición tratada, la ruta de administración y la edad y

condición del paciente y finalmente será del criterio del medico que atiende. En general las dosis empleadas para tratamiento humano adulto típicamente estarán en el rango entre 2 y 800 mg por día, dependiendo de la ruta de administración. 195

Por lo tanto para administración parenteral una dosis diaria típicamente estára en el rango entre 2 y 50 mg, preferiblemente entre 5 y 25 mg por día. Para administración oral una dosis diaria tipicamente estará dentro del rango 10 y 800 mg, ej., entre 20 y 150 mg por día.

La dosis deseada se puede presentar convenientemente en una única dosis o como dosis divididas administradas a intervalos apropiados, por ejemplo dos, tres, cuatro o más sub- dosis por día.

Composiciones

Mientras es posible que, para uso en terapia un compuesto del invento se puede administrar como el compuesto químico crudo, es preferible presentar el ingrediente activo como una formulación farmacéutica.

Por lo tanto el invento suministra una composición farmacéutica que comprende al menos una entidad química que comprende un compuesto de la Formula (IA) o Formula (A') y derivados fisiológicamente aceptables del mismo y un vehiculo o diluyente farmacéuticamente aceptable. La formulación opcionalmente puede contener otros ingredientes terapéuticos y/o profilácticos. El vehiculo debe ser "aceptable" en el sentido de ser compatible con otros ingredientes de la formulación y no perjudiciales al receptor del mismo.

Las composiciones del invento incluyen aquellas en una forma especialmente formulada para administración oral, bucal, parenteral, inhalación o insuflacción, implante o administración rectal.

Las tabletas y cápsulas para administración oral pueden contener excipientes convencionales tales como agentes aglomerantes, por ejemplo, jarabe, acacia, gelatina, sorbitol, tragacanto, mucilago de almidón o polivinilpirrolidona; rellenos, por ejemplo, lactosa, azúcar, celulosa microcristalina, almidón de maiz, fosfato de calcio o sorbitol; lubricantes, por ejemplo, estearato de magnesio, ácido estearico, talco, glicol de polietileno o sílice; desintegrantes, por ejemplo, glicolato de

almidón de papa o almidón de sodio, o agentes humectantes tales como laurilsulfato sódico. Las tabletas se pueden recubrir según métodos bien conocidos en el estado de la técnica. Las preparaciones líquidas orales pueden estar en la forma de, por ejemplo, suspensiones acuosas o aceitosas, soluciones, soluciones, emulsiones, jarables o elixires, o se pueden presentar como un producto seco para constitución con agua u otro vehiculo apropiado antes de uso. Tales preparaciones líquidas pueden contener aditivos convencionales tales como agentes de suspensión, por ejemplo, jarabe de sorbitol, metilcelulosa, jarabe de glucosa/azúcar, gelatina, hidroxietilcelulosa, carboximetilcelulosa, gel de estearato de aluminio o grasas comestibles hidrogenadas; agentes emulsificantes, por ejemplo, lecitina, mono- oleato de sorbitan o acacia; vehículos no acuosos (los cuales pueden incluir aceites comestibles) , por ejemplo, aceite de almendras, aceite de coco fraccionado, ésteres aceitosos, glicol de propileno o alcohol etílico; solubilizantes tals como surfactantes por ejemplo polisorbatos u otros agentes tales como ciclodextrinas; y preservativos, por ejemplo, p- hidroxibenzoatos de metilo o propilo o ácido ascórbico. Las composiciones también se pueden formular como supositorios, ej., conteniendo bases supositorias convencionales tales como manteca de cacao u otros gliceridos.

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

La composición según el invento se puede formular para administración parenteral mediante inyección o infusión continua. Las formulaciones para inyección se pueden presentar en forma de dosis unitarias en ampollas, o recipientes de multiples dosis con un preservativo agregado. Las composiciones pueden tomar tales formas como suspensiones, soluciones, o emulsiones en vehículos aceitosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilización y/o dispersión. Alternativamente el ingrediente activo puede estar en forma de polvo para constitución con un vehículo apropiado, ej., agua estéril, libre de pirógenos antes de utilizar.

Las composiciones según el invento pueden contener entre 0.1- 99% del ingrediente activo, convenientemente entre 30- 95% de tabletas y cápsulas y 3- 50% para preparaciones líquidas.

Puesto que los compuestos del invento están diseñados para utilizar en composiciones farmacéuticas, fácilmente se entenderá que estos se proporcionan preferiblemente en forma sustancialmente pura, por ejemplo al menos 60% puros, más apropiadamente al menos 75% puros y preferiblemente al menos 85% puros, especialmente al menos 98% puros (El porcentaje es sobre una base por peso) . Las preparaciones impuras de los compuestos se pueden utilizar para preparar las formas más puras utilizadas en las composiciones farmacéuticas; estas preparaciones menos puros de los compuestos deben contener al menos 1%, más preferiblemente al menos 5% y preferiblemente entre 10 y 59% de un compuesto del invento.

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Ejemplos de Farmacia

Tabletas

a)

Compuesto del invento	50.0 mg
Lactosa	70.0 mg
Celulosa microcristalina	70.0 mg
Polivinilpirrolidona entrelazada	8.0 mg
Estearato de magnesio	2.0 mg
Peso de compresión	200.0 mg

El compuesto del invento, celulosa microcristalina, lactosa y polivinilpirrolidona entrelazada se tamizan a través de un tamiz de 500 micras y se mezclan en un mezclador apropiado. El estearato de magnesio se tamizó a través de un tamiz de 250 micras y se mezcló con la mezcla activa. La mezcla se comprimió en las tabletas utilizando troqueles apropiados.

b)

Compuesto del invento	50.0 mg
Lactosa	120.0 mg
Almidón pregelatinizado	20.0 mg
Polivinilpirrolidona entrelazada	8.0 mg
Estearato de magnesio	2.0 mg
Peso de compresión	200.0 mg

El compuesto del invento, lactosa y almidón pregelatinizado se mezclan juntos y se granulan con agua. La masa húmeda es secada y molida. El estearato de magnesio y polivinilpirrolidona entrelazada se clasifican a través de un tamiz de 250 micras y se mezclan con el granulo. La mezcla resultante se comprime utilizando troqueles para tabletas apropiados.

Capsulas

a)	Compuesto del invento	50.0mg
	Lactosa	148.0mg
	Estearato de Magnesio	2.0mg
	Peso de relleno	200.0mg

El compuesto del invento y almidón pregelatinizado se clasifican a través de un tamiz o rejilla de 500 micras mesh, se mezclan juntos y se lubrican con estearato de magnesio, (tamizado a través de un tamiz de 250 micras) . La mezcla es llenada en cápsulas de gelatina dura de un tamaño adecuado.

b)	Compuesto del invento	50.0mg
	Lactosa	132.0mg
	Polivinilpirrolidona	8.0mg
	Polivinilpirrolidina entrelazada	2.0mg
	Peso total	200.0mg

El compuesto del invento y lactosa se mezclan juntos y se granulan con una solución de polivinilpirrolidona. La masa húmeda es secada y molida. El estearato de magnesio y polivinilpirrolidona entrelazada se clasifican a través de un tamiz de 250 micras y se mezclan con los gránulos. La mezcla resultante es llenada en capsulas de gelatina dura de un tamaño adecuado.

Formulación de Inyección	**% w/v**
Compuesto del invento	0.10

Agua para inyección B.P. a 100.00

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El cloruro de sodio se puede agregar para ajustar la tonicidad de la solución y el pH se puede ajustar a aquel de máxima estabilidad y/o para facilitar solución del compuesto del invento utilizando ácido o alcalino diluido o mediante la adición de sales buffer apropiadas. También se pueden agregar solubilizantes, tales como cosolventes para facilitar solución del compuesto del invento. También se pueden incluir antioxidantes y sales quelantes metálicas. La solución es clarificada, compuesta a volumen final con agua y el pH medido nuevamente y ajustado si es necesario, para proporcionar 1,g/ml del compuesto de la Formula (I) o Formula (A) . La solución se pueden empacar para inyección, por ejemplo mediante llenado y sellado en ampollas, frascos y jeringas. Las ampollas, frascos o jeringas se pueden llenar de manera aséptica (ej., la solución se puede esterilizar mediante filtración y llenar en ampollas estériles bajo condiciones asépticas y/o esterilizar de manera Terminal (ej., mediante calentamiento en autoclae utilizando uno de los ciclos aceptables) . La solución se puede empacar bajo una atmósfera inerte de nitrógeno.

Preferiblemente la solución es llenada en ampollas, selladas por fusión del vidrio y esterilizadas de manera terminal.

Formulaciones estériles adicionales son preparadas de manera similar conteniendo 0.05, 0.20 y 0.5% w/v del compuesto del invento, para proporcionar respectivamente 0.5, 2 y 5mg/ml del compuesto del invento.

Los compuestos del invento también se pueden utilizar en combinación con otros agentes terapéuticos. Por lo tanto, el invento proporciona en un aspecto adicional, una combinación que comprende un compuesto del invento o un derivado farmacéuticamente aceptable del mismo junto con un agente terapéutico adicional.

Cuando un compuesto del invento o un derivado farmacéuticamente aceptable del mismo se utiliza en combinación con un segundo agente terapéutico activo contra la misma condición patológica, la dosis de cada compuesto puede diferir con relación a aquella cuando el compuesto se utiliza solo. Dosis apropiadas serán fácilmente apreciadas por aquellos con experiencia en el

estado de la técnica. Se apreciará que la cantidad de un compuesto del invento requerido para utilizar en tratamiento variará con la naturaleza de la condición tratada y la edad y condición del paciente y finalmente será según el criterio del medico o veterinario encargado. Los compuestos del presente invento se pueden utilizar en combinación con tocoliticos o medicinas profilácticas. Estos incluyen, pero no están limitados a, beta- agonistas tales como terbutalina o ritodrina, bloqueadores de canales de calcio, ej., nifedepina, fármacos anti- inflamatorios no esferoidales, tales como indometacina, sales de magnesio, tales como sulfato de magnesio, otros antagonistas de oxitocina, tales como atosigan, y agonistas de progesterona y formulaciones. Además, los compuestos del presente invento se pueden utilizar en combinaciones con esteroides antenatales incluyendo betametasona y dexametasona, vitaminas prenatales especialmente suplementos de folato, antibioticos, incluyendo pero sin limitar a ampicilina, amoxicilina/clavulanato, metronidazol, clindamicina, y anxiolíticos.

Las combinaciones citadas anteriormente se pueden presentar convenientemente para utilizar en la forma de una formulación farmacéutica y por lo tanto las formulaciones farmacéuticas que comprenden una combinación como se definió anteriormente junto con un vehiculo farmacéuticamente aceptable o excipiente comprenden un aspecto adicional del invento. Los componentes individuales de tales combinaciones se pueden administrar ya sea de manera secuencial o simultánea en formulaciones farmacéuticas separadas o combinadas mediante cualquier ruta conveniente.

Cuando la administración es secuencial, cualquiera el compuesto del presente invento o el segundo agente terapéutico se puede administrar primero. Cuando la administración es simultanea, la combinación se puede administrar ya sea en la misma o diferente composición farmacéutica. Cuando se combinan en la misma formulación se apreciará que los dos compuestos deben ser estables y compatibles entre sí y los otros componentes de la formulación. Cuando se formulan de manera separada estos se pueden proporcionar en cualquier formulación conveniente, convenientemente en tal forma como se conocen para tales compuestos en el estado de la técnica.

Abreviaturas

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Al describir el invento, los elementos químicos se identifican según la Tabla Periódica de los Elementos. Las abreviaturas y símbolos utilizados en la presente están de acuerdo con la utilización común de tales abreviaturas y símbolos por aquellos con experiencia en los estados de las técnicas químicas. Las siguientes abreviaturas se utilizan en la presente:

BOC	tert- butiloxicarbonilo
Cbz	benciloxicarbonilo
CDCl3	cloroformo deuterado
CDM	diclorometano
DIPEA	diisopropilamina
Dioxan	1,4- dioxan
DMF	N,N- dimetilformamida
DMSO	dimetilsulfóxido
DMSO- d6	dimetilsulfóxido deuterado
EDC.HCl	hidrocloruro de 1- (3- dimetilaminopropil) - 3- etilcarboxiimida
ES+ MS	Espectroscopía de masas por electrospray Positivo
h	horas
ES- MS	Espectroscopía de masas por electrospray negativo
HATU	Hexafluorofosfato de O- (7- azabenzotriazol- 1- il) - N,N,N',N'- tetrametiluronio
HPLC	Cromatografía líquida de alta presión
LCMS	Espectrometria de Masa de Cromatografía Líquida
Mesilato	metilsulfonato
Min	minutos
NMP	N- metilpirrolidona
NMR	Espectroscopia de Resonancia Magnética Nuclear
Pd/C	paladio sobre carbono
Rt	tiempo de retención
RT	temperatura ambiente
SPE	extracción de fase sólida
TBDMSO	tert- butildimetilsililoxilo

TFA ácido trifluoroacético

tosilato4- toluensulfonato

Xantphos 4,5- bis(difenilfosfino) - 9,9- dimetilxanteno

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Preparación de Compuestos

Los compuestos del invento se pueden preparar en forma conocida en una variedad de formas. En los siguientes esquemas de reacción y de aquí en adelante, a menos que se indique lo contrario R1 a R12, A, n y m son como se definieron anteriormente para la Formula (I) o Formula (A) , y el anillo B representa un grupo mono- , bi- o triciclito que contiene uno o más heteroátomos independientemente seleccionados de O, S o N, por ejemplo un anillo fenilo, pirazol o piridinilo. Estos procesos forman aspectos adicionales del invento.

En toda la especificación, las formulas generales se designan mediante numerales romanos (I) , (II) , (III) , (IV) , etc, con la excepción de la Formula (A) . Subgrupos de compuestos de las Formulas (I) y (A) se definen como (Ia) , (Aa) , (Ib) , (Ab) , (Ic) , (Ac) , (Id) , (Ad) , (Ie) , (Ae) , (If) , (Af) , (Ig) , (Ag) , (If) , (Af) , (Ii) , (Ai) , (lj) , (Aj) , (lk) , (Ak) , (lm) , (Am) , (ln) , (An) , (lo) , (Ao) , (lp) , (Ap) , (lq) y Aq) .

Los compuestos de la Formula (I) o Formula (A) , se pueden preparar según el Esquema de reacción general 1 mediante los siguientes pasos como se indicó en el Esquema:

Paso (a)

Una reacción entre un ácido carboxílico N- protegido de la Formula (II) , en donde P representa un grupo protector de nitrógeno apropiado, por ejemplo alcoxicarbonilo (ej., tert-butoxicarbonilo) , o Cbz; una amina apropiada de la Formula (III) , un aldehido (IV) y un isonitrilo (V) , en donde J es sustituyente opcional, por ejemplo, J es un sustituyente de cloro, benciloxilo o TBDMSO o está ausente, en un solvente apropiado tal como metanol, trifluoroetanol o cloroformo para proporcionar los compuestos de la Formula (VI) , en donde J es un sustituyente opcional, por ejemplo, J es un sustituyente de cloro, benciloxilo o TBDMSO o está ausente.

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Será manifiesto para una persona con experiencia en el estado de la técnica que los compuestos de la Formula (II) , (III) , (IV) y (V) se pueden agregar en orden variable, por ejemplo se puede formar una imina entre aldehido (IV) y amina (III) antes de la adición de ácido carboxílico (II) e isonitrilo (IV) , o los reactivos se pueden agregar en una mezcla "de vasija única" ("one- pot") .

Además será manifiesto para la persona con experiencia que la amina (III) se puede agregar a la reacción en la forma de una sal, tal como una sal de hidrocloruro; en tal caso se puede agregar una base a la mezcla de reacción, por ejemplo trietilamina o DIPEA.

Paso (b)

Una reacción de desprotección para retirar el grupo protector de nitrógeno P de los compuestos de la Formula (VI) para proporcionar compuestos de la Formula (VII) , en donde J es un sustituyente opcional, por ejemplo, J es un sustituyente de cloro, benciloxilo o TBDMSO o está ausente. Cuando P es un grupo alcoxicarbonilo (ej., *tert*- butoxicarbonilo) , la desprotección se puede realizar utilizando un ácido apropiado, por ejemplo TFA o HCl en un solvente apropiado tal como 1,4- dioxan o metanol, o en la presencia de cloruro de acetilo en metanol. Cuando P es un grupo CBz, la desprotección se puede realizar mediante hidrogenación en presencia de un catalizador adecuado, por ejemplo Pd/C, en un solvente apropiado tal como ácido acético o metanol.

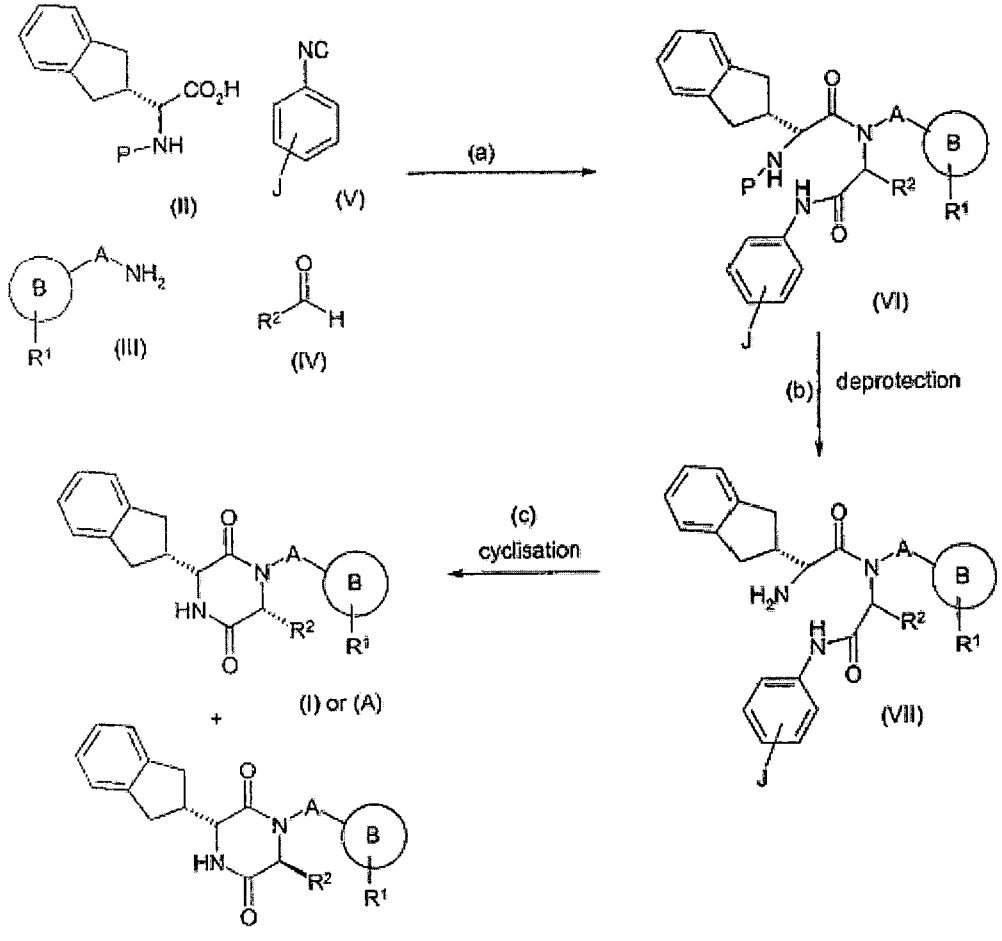
Paso (c)

Una reacción de ciclización de los compuestos de la Formula (VII) para proporcionar compuestos de la Formula (I) o Formula (A) . La ciclización se puede realizar en presencia de un ácido apropiado tal como ácido acético glacial, en un solvente apropiado tal como cloroformo. Alternativamente, la ciclización se puede realizar en presencia de una base adecuada, tal como bicarbonato de sodio, o una mezcla de bicarbonato de sodio y trietilamina. Alternativamente, la ciclización se puede realizar en ausencia de ácido o base en un solvente apropiado.

Será manifiesto para una persona con experiencia en el estado de la técnica que el cis-diastereoisomero, es decir, el compuesto de la formula (I) o Formula (A) , se puede separar del

trans diastereoisomero (ambos isómeros se muestran en el Esquema 1) mediante técnicas convencionales de purificación, por ejemplo mediante cromatografía. Alternativamente, la mezcla de cis- y trans- diastereoisomeros puede estar sujeta a interconversiones de grupos funcionales, por ejemplo aquellos ilustrados en los Esquemas de reacción 3 a 12 a continuación, y separados mediante técnicas convencionales.

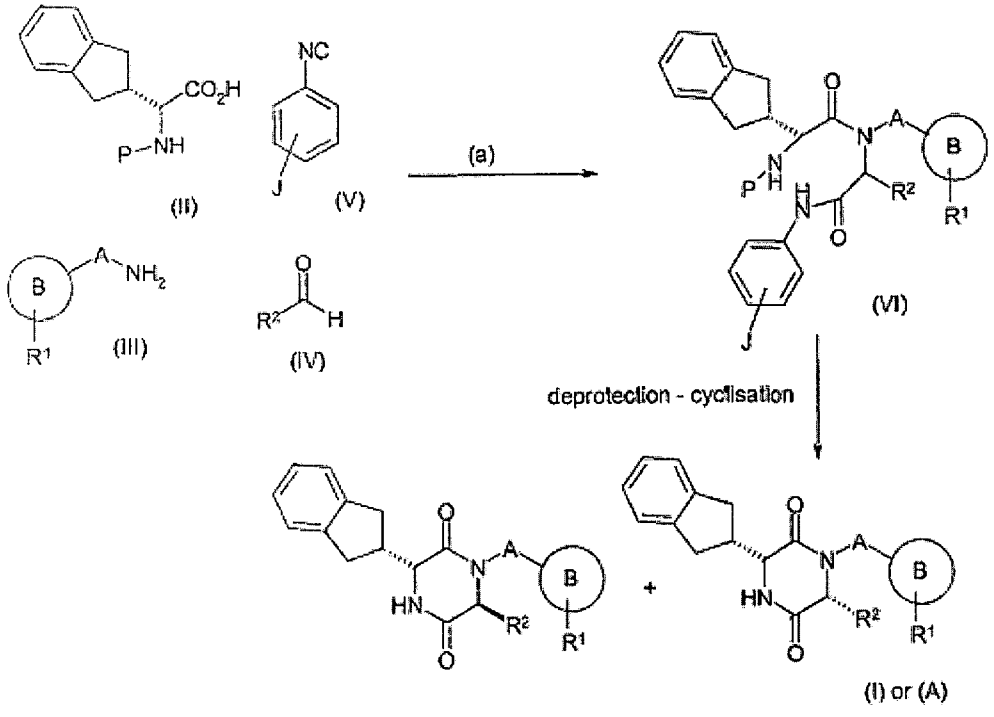
Esquema 1



Alternativamente, cuando P es un grupo alcoxicarbonilo (ej., tert- butoxicarbonilo) , el paso de desprotección y el paso de ciclización se pueden realizar en una reacción de un paso como se muestra en el Esquema 2, en presencia de un ácido apropiado, por ejemplo HCl, en un solvente adecuado, por ejemplo una mezcla de 1,4- dioxano y DCM.

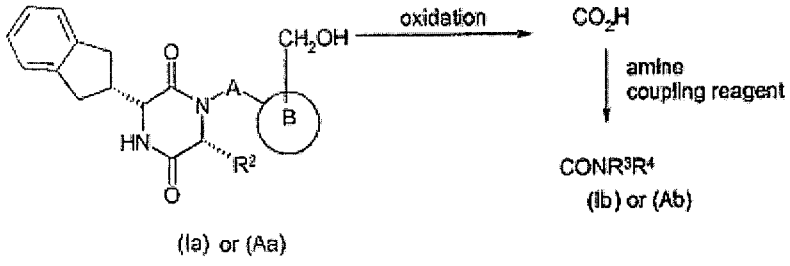
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Esquema 2



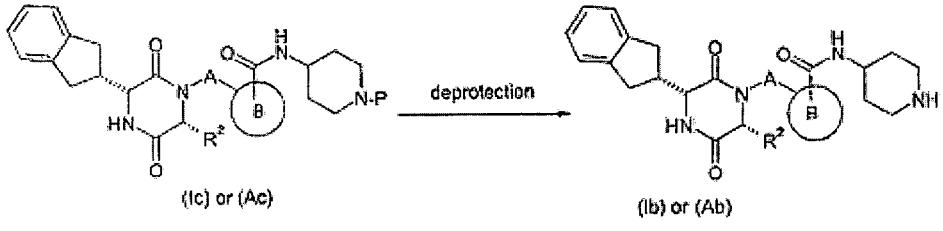
Los compuestos de la Formula (Ib) o Formula (Ab) , en donde R^1 representa –CONR3R4, se pueden preparar a partir de compuestos de la Formula (Ia) o Formula (Aa) , en donde R1 representa $-CH_2OH$, según el esquema de reacción 3. Los compuestos (Ia) y (Aa) se puede oxidizar en la posición R1 al grupo de ácido carboxílico $-CO_2H$. Esto se puede realizar por ejemplo en un proceso de dos pasos mediante reacción de los compuestos de la Formula (Ia) o (Aa) con N- oxido de 4- metilmorfolino (NMNO) con perrutenato de tetrapropilamonio (TPAP) en un solvente apropiado tal como diclorometano, seguido por oxidación del aldehido resultante utilizando un agente oxidante adecuado, tal como clorito de sodio, para proporcionar el ácido carboxílico. Luego el ácido carboxílico puede reaccionar con una amina apropiada HNR3R4, por ejemplo en presencia de un agente acoplador, tal como tetrafluoroborato de 2- (1H- benzotriazol- 1- il) - 1,1,3,3- tetrametiluronio en presencia de una base apropiada tal como trietilamina, en un solvente ej., diclorometano para formar los compuestos de la Formula (Ib) o Formula (Ab) .

Esquema 3



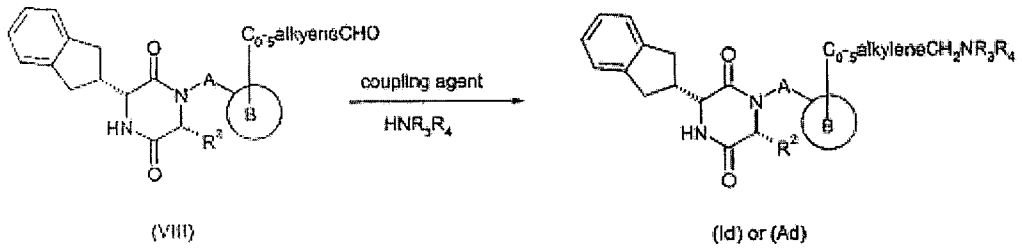
Los compuestos de la Formula (Ib) o formula (Ab) , en donde R^1 representa el grupo – CONR3R4, en donde cualquiera entre R3 o R4 representa un grupo que contiene una fracción NH, por ejemplo un grupo heterociclilo que contiene nitrógeno, ej., piperidina, se puede preparar según el Esquema de reacción 4 (piperidina mostrada a manera de ejemplo) al desproteger el compuesto N- protegido correspondiente de la Formula (Ic) o (Ac) , en donde P es un grupo protector de nitrógeno apropiado. Donde P es, por ejemplo, un grupo alcoxicarbonilo (ej., *tert*-butoxicarbonilo) , la desprotección se puede realizar en presencia de ún ácido, ej., HCl, en un solvente apropiado tal como 1,4- dioxano.

Esquema 4



Los compuestos de la Formula (Id) o (Ad) , en donde R1 representa C1- 6alquilo sustituido por el grupo _NR3R4 se puede preparar según el Esquema de reacción 5 al reaccionar un compuesto aldehido de la Formula (VIII) con un agente acoplador apropiado, tal como triacetoxiborohidruro de sodio, en presencia de una amina apropiada HNR3R4.

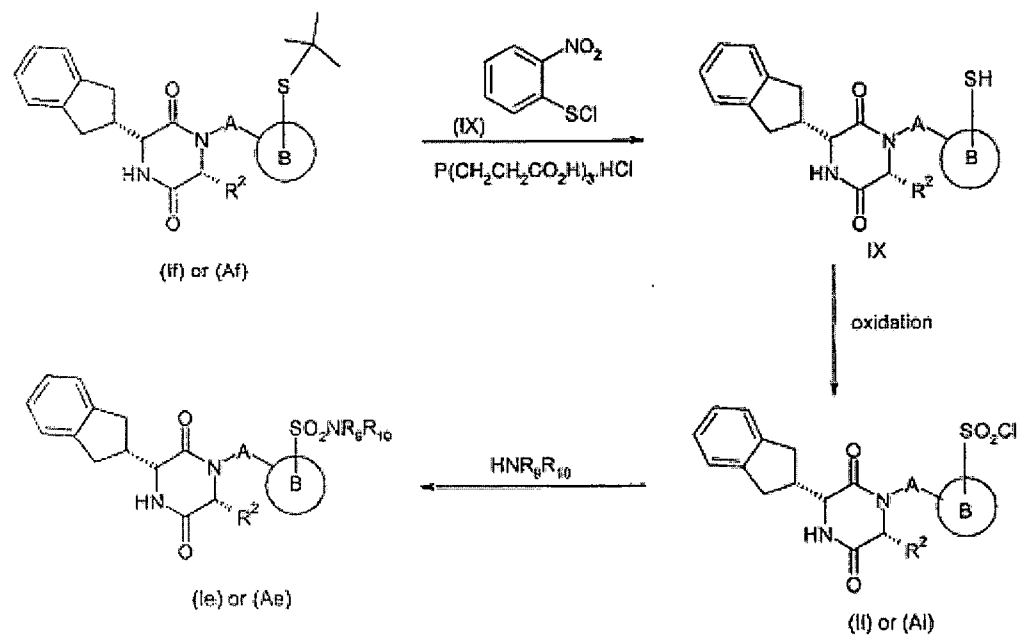
Esquema 5



(VIII) (Id) or (Ad)

Los compuestos de la Formula (Ie) o Formula (Ae) , en donde R1 representa el grupo –S(O) mNR9R10, se pueden preparar según el Esquema de reacción 6 al desproteger los compuestos de sulfanilo de la Formula (If) o (Af) para formar el compuesto tiol IX. Esto se puede realizar por ejemplo utilizando un cloruro de nitroaril sulfenilo, por ejemplo cloruro de 2-nitrobencenosulfenilo, en presencia de una base apropiada, tal como trietilamina, y un solvente apropiado, por ejemplo DMF, e hidrocloruro de tris(carboxietil) fosfina. El compuesto IX se puede oxidar, ej., con cloruro de sulfurilo en presencia de una base apropiada, tal como nitrato de potasio, para formar un compuesto de cloruro de sulfonilo de la Formula (Ii) o (Ai) la cual subsecuentemente reacciona con una amina apropiada HNR^9R^{10} para formar la amida (Ie) o (Ae).

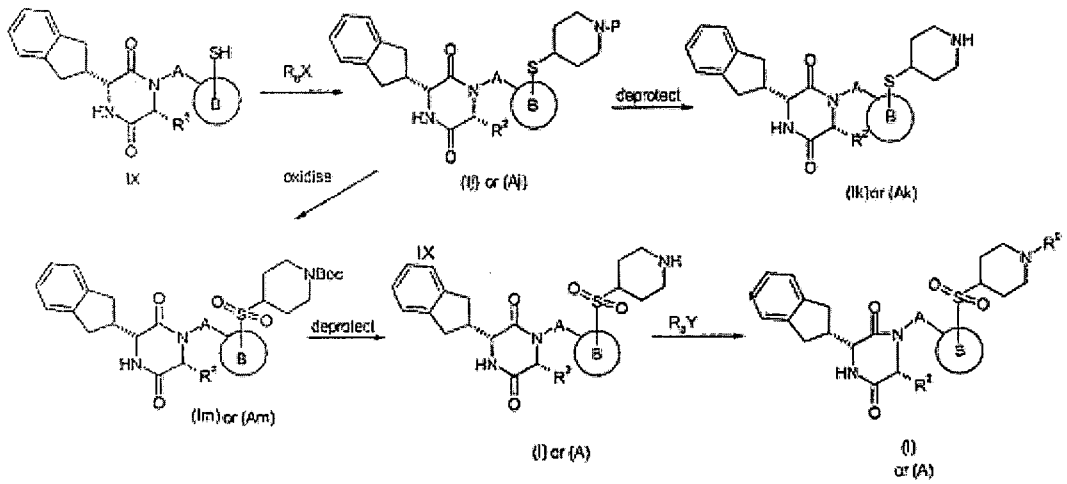
Esquema 6



(If) or (Af) (Ie) or (Ae) (Ii) or (Ai)

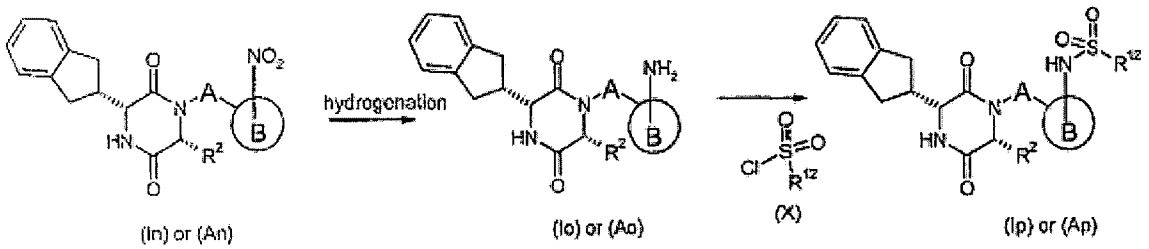
Los compuestos de la Formula (I) o Formula (A) , en donde R1 representa el grupo –S(O) nR6 se pueden preparar según el Esquema de Reacción 7 comenzando a partir del compuesto tiol de la Formula IX. Este se puede reaccionar con una amina N- protegida apropiada R^6X, en donde X es un grupo saliente apropiado, por ejemplo mesilato, tosilato o halo para formar un compuesto sulfanilo de la Formula (Ij) o (Aj) , en donde P es un grupo protector de nitrógeno, el cual se puede ya sea oxidizar a la sulfota (Im) o (Am) utilizando un agente oxidante adecuado tal como ácido 3- cloroperoxibenzoico, o simplemente desproteger, por ejemplo utilizando un ácido, donde P es un grupo *tert*- butoxicarbonilo, para formar un compuesto de sulfanilo de la Formula (Ik) o (Ak) . La sulfota (Im) o (Am) se puede desproteger, por ejemplo utilizando un ácido, donde P es un grupo tert- butoxicarbonilo, y se puede adicionalmente modificar, si se desea, para introducir un grupo apropiado R9 sobre la amina, mediante tratamiento con R9Y, en donde Y es un grupo saliente apropiado, por ejemplo mesilato, tosilato o halo, en presencia de una base apropiada, por ejemplo carbonato de potasio, en un solvente apropiado, tal como DMF.

Esquema 7



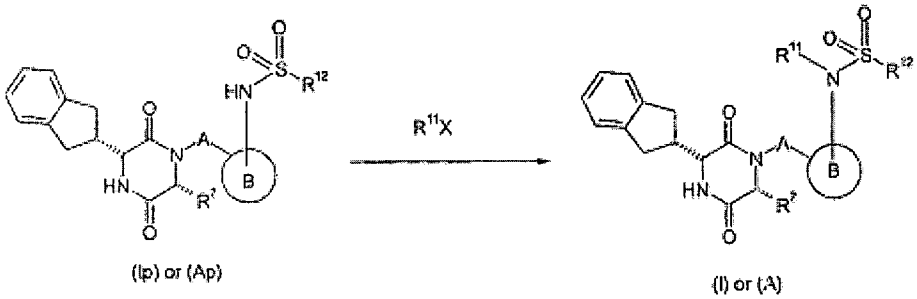
Los compuestos de la Formula (I) o Formula (A) , en donde R1 representa el grupo –NR11S(O) mR12, en donde R11 representa H, se pueden preparar según el Esquema de Reacción 8 comenzando a partir del compuesto nitro (In) o (An) el cual se puede hidrogenar utilizando condiciones estándares, por ejemplo en presencia de un catalizador Pd/C para formar la amina (Io) o (Ao) el cual se puede reaccionar con un compuesto de cloruro de sulfonilo apropiado de la Formula (X) en presencia de una base adecuada, tal como trietilamina y dimetilaminopiridina para formar el compuesto de sulfonamida (Ip) o (Ap) .

Esquema 8



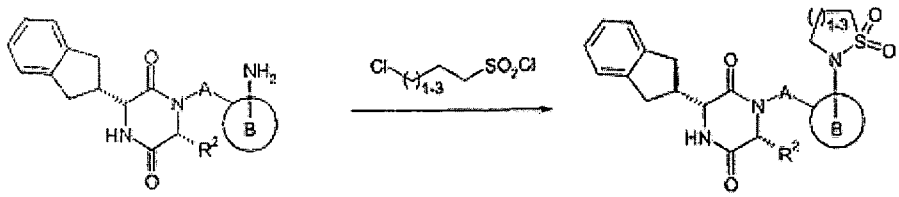
Alternativamente, los compuestos de la Formula (I) o Formula (A) , en donde R1 representa en grupo –NR11S(O) mR12, en donde R11 representa un grupo C1- 4alquilo opcionalmente sustituido, se pueden preparar según el Esquema de reacción 9 al reaccionar la sulfonamida (Ip) o (Ap) con un haluro de alquilo apropiado R11Z, en donde Z es un grupo saliente tal como halógeno, por ejemplo R11Z es yodometano, en presencia de una base apropiada, tal como carbonato de potasio en un solvente apropiado tal como dimetilformamida (DMF) .

Esquema 9



Los compuestos de la Formula (I) o Formula (A) , en donde R1 representa el grupo –NR11S(O) mR12 el cual forma una sulfonamida ciclizada, se pueden preparar según el Esquema de Reacción 10 comenzando a partir del correspondiente compuesto de amina (Io) o (Ao) y reaccionado este con el cloruro de sulfonilo de cloroalquilo apropiado en presencia de un catalizador apropiado tal como yoduro de tretrabutil amonio.

Esquema 10

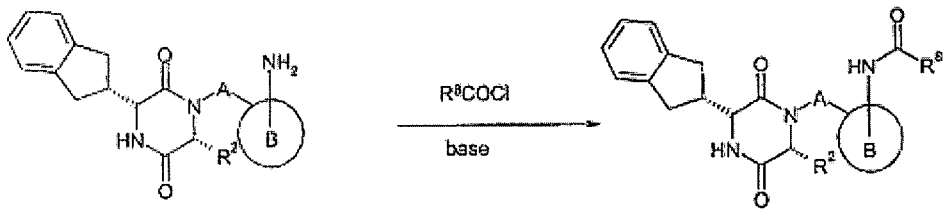


(Io) or (Ao) (I) or (A)

210

Los compuestos de la Formula (I) o Formula (A) , en donde R1 representa el grupo $-NR^7COR^8$ se pueden preparar según el Esquema de Reacción 11 al tratar el compuesto de amina primario de la Formula (Io) o (Ao) con un cloruro ácido apropiado, tal como cloruro de acetilo, en presencia de un solvente apropiado, tal como diclorometano, y una base, por ejemplo piridina.

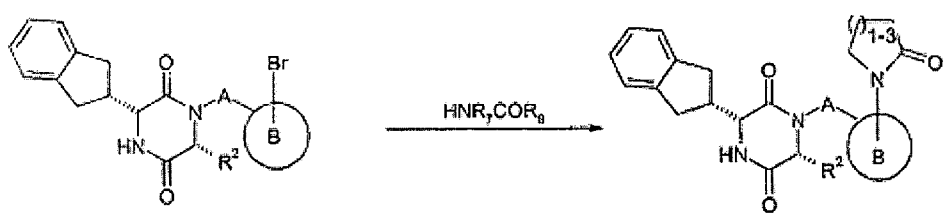
Esquema 11



(Io) or (Ao) (I) or (A)

Los compuestos de la Formula (I) o Formula (A) , en donde R1 representa el grupo –NR7COR8, en donde R^7 y R^8 junto con el grupo carbonilo al cual están unidos forman un grupo cíclico, se pueden preparar según el Esquema de reacción 12 reaccionando el compuesto de bromo (Iq) o (Aq) con una amida apropiada, HNR^7COR^8, en donde R7 y R8 junto con el grupo carbonilo al cual están unidos forman un grupo cíclico, en presencia de un catalizador apropiado tal como yoduro de cobre en un solvente apropiado, tal como 1,4- dioxano y la mezcla se sometió a irradiación microondas para formar la amida cíclica resultante.

Esquema 12



(Iq) or (Aq) (I) or (A)

Aquellos con experiencia en el estado de la técnica apreciarán que donde un compuesto de la Formula (I) o (A) posee un grupo amida en cualquier parte en la molécula, por ejemplo el grupo $-CONR^3R^4$ en la posición R^1, este grupo se puede sintetizar por ejemplo a partir de una reacción de acople entre el correspondiente ácido carboxílico –CO2H y una amina HNR^3R^4, utilizando una variedad de métodos estándares. El ácido carboxílico se puede sintetizar mediante oxidación del correspondiente aldehido –CHO o el correspondiente alcohol –CH2OH, o mediante hidrólisis del éster correspondiente –CO2Rx, en donde Rx es por ejemplo un grupo C1- 4alquilo, o a partir del correspondiente compuesto halo, por ejemplo mediante el tratamiento con un reactivo Grinard en presencia de dióxido de carbono.

Aquellos con experiencia en el estado de la técnica apreciarán que donde un compuesto de la Formula (I) o (A) posee una sulfonamida en cualquier parte en la molécula, por ejemplo el grupo $-SO2NR^9R^{10}$, este grupo se puede sintetizar por ejemplo a partir de una reacción entre el correspondiente cloruro de sulfonilo $-SO_2Cl$ y una amina, utilizando una variedad de métodos estándares. El cloruro de sulfonilo –SO2Cl se puede sintetizar mediante oxidación del correspondiente compuesto tiol –SH utilizando condiciones estándares, ej., reacción con cloruro de sulfurilo en presencia de una base apropiada. El compuesto tiol –SH es accesible a partir de los correspondientes compuestos de sulfanilo –SC1- 4alquilo al realizar la reacción de desprotección bajo condiciones estándares.

Aquellos con experiencia en el estado de la técnica apreciará además que donde un compuesto de la Formula (I) o (A) posee un sulfoxido o sulfota en cualquier parte en la molécula, por ejemplo el grupo $-S(O)\ 1\text{-}\ 2R^6$, este grupo se puede sintetizar por ejemplo mediante una reacción de oxidación del correspondiente compuesto de sulfanilo $-SR^6$ bajo condiciones estándares. Por ejemplo, oxidación del compuesto de sulfanilo $-SR^6$ para proporcionar el compuesto de sulfota –SO2R6 se puede realizar utilizando un agente de oxidación apropiado tal como ácido 3-cloroperoxibenzóico. El compuesto de sulfanilo –SR6 es accesible mediante alquilación del correspondiente compuesto tiol –SH con un agente alquilante R6X, en donde X es un grupo saliente apropiado, por ejemplo mesilato, tosilato o halo, bajo condiciones estándares.

Aquellos con experiencia en el estado de la técnica apreciarán que en la preparación del compuesto de la Formula I o un solvato del mismo, puede ser necesario y/o deseable proteger uno o más grupos sensibles en la molécula o el intermedio apropiado para prevenir reacciones secundarias indeseadas. Grupos protectores apropiados para utilizar según el presente invento son bien conocidos por aquellos con experiencia en el estado de la técnica y se pueden utilizar en una forma convencional. Ver, por ejemplo, "Grupos protectores en síntesis orgánica" de T.W. Greene y P.G.M. Wuts (John Wiley & Sons 1991) o "Grupos Protectores" de P.J. Kocienski (Georg Thieme Verlag 1994) . Ejemplos de grupos protectores amino apropiados incluyen grupos protectores del tipo acilo (ej., formilo, trifluoroacetilo, acetilo) , grupos protectores tipo uretano aromático (ej., benciloxicarbonilo (Cbz) y Cbz sustituido) , grupos protectores de uretano alifático (ej., 9- fluorenilmetoxicarbonilo (Fmoc) , t- butiloxicarbonilo (Boc) , isopropiloxicarbonilo, ciclohexiloxicarbonilo) y grupos protectores tipo alquilo o aralquilo (ej., bencilo, tritilo, clorotritilo) . Ejemplos de grupos protectores de oxigeno apropiados pueden incluir por ejemplo grupos alquilo, sililo, tales como trimetilsililo o tert- butildimetilsililo; éteres de alquilo tales como tetrahidropiranilo o tert- butilo; o ésteres tales como acetato.

Ejemplos

Los siguientes ejemplos ilustran el invento. Estos ejemplos no pretenden limitar el alcance del invento, sino proporcionar guía al artesano hábil para preparar y utilizar los compuestos, composiciones, y métodos del invento. Mientras se describen realizaciones particulares del invento, el artesano hábil apreciará que varios cambios y modificaciones se pueden realizar sin apartarse del espíritu y alcance del invento.

Purificación General y Métodos Analíticos

Se realizó HPLC analítica mediante uno de los siguientes métodos:

A) Sobre una columna Supelcosil LCABZ+PLUS (3.3 cm x 4.6 mm ID) , eluyendo con 0.1% HCO2H y 0.01 M acetato de amonio en agua (solvente A) , y 0.05% HCO2H y 5% agua en acetonitrilo (solvente B) , utilizando el siguiente gradiente de elución 0- 0.7 minutos 0%B a una tasa de flujo de 3ml/min.

B) Sobre un LC Acquity Ultra Performance equipado con una columna Acquity UPLC BEH C18 1.7 um (50 x 2.1 mm, i.d.) , eluyendo con 0.05% TFA en agua (solvente A) y 0.05% TFA en acetonitrilo (solvente B) , utilizando el siguiente gradiente de elusión 5- %- 95% (solvente B) sobre 0.65 minutos y manteniendo a 95% durante 0.35 min a una tasa de flujo de 0.8 ml/minuto.

C) Sobre HPLC Shimadzu LC- 2010 equipada con una columna YMC- AQ (50x2.0 mm ZD) , eluyendo con 0.1% TFA en agua (solvente A) y 0.05% TFA en acetonitrilo (solvente B) , utilizando el siguiente gradiente de elusión 10% - 80% (solvente B) durante 3.0 minutos y manteniendo a 80% durante 0.5 minutos a una tasa de flujo de 0.8 ml/minuto.

D) Sobre una columna Agilent Zorbax SB- C18 5.0 µm (2.1 mm x 50 mm, i.d.) eluyendo con 0.05% TFA en agua (solvente A) y 0.05% TFA en acetronitrilo (solvente B) , utilizando el siguiente gradiente de elusión 10% - 99% (solvente B) durante 3.0 min y manteniendo a 99% durante 1.0 min a una tasa de flujo de 1.0 mL/min.

Los espectros de masa (MS) se registraron sobre un espectrómetro de Plataforma Fisons VG o de micromasa Waters ZQ o Finnigan LCQ- Advantage utilizando modos de electroatomización positiva [(ES+ve para proporcionar iones moleculares MH^+ y $M(NH4)^+$] o electroatomización negativa [(ES- ve para proporcionar ión molecular $(M- H)^-$] sobre una Micromasa serie 2 o un espectrómetro de masa Waters ZQ. Los espectros ^1H NMR se registraron utilizando un espectrómetro Broker DPX o Avance 300MHz o Avance 400MHz utilizando tetrametilsilano como el estándar externo.

La cromatografía de columna de sílice se refiere a purificación realizada utilizando cartuchos de fase normal de sílice preempacada (Redisep®) vendidos por Isco o cartuchos SPE (extracción de fase sólida) vendidos por internacional Sorbent Technology Ltd. SPE de aminopropilo y SCX- SPE se refieren a los cartuchos de aminopropilo y flash SCX- 2 vendidos por Internacional Sorbent Technology Ltd. Purificación Wilson se refiere a la purificación realizada por cromatografía líquida de alto desempeño sobre una columna Xterra Prep RP18 5 um (30 mm x 100 mm i.d.) eluyendo con 0.1 TFA en agua y 0.1% TFA en acetonitrilo utilizando un gradiente de elusión a una tasa de flujo de 25 ml/min.

Autopreparación dirigida de masa se refiere a métodos donde el material se purificó mediante cromatografía líquida de alto desempeño sobre una columna HPLCABZ+ 5um (5cmx10mm i.d.) con 0.1% HCO2H en agua y 95% MeCN, 5% agua (0.5% HCO_2H) utilizando gradiente de elusión a una tasa de flujo de 8ml/min. El recolector de fracción Wilson 202 se activó mediante un Espectrómetro de Masa de Plataforma VG al detectar la masa de interés.

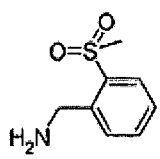
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Fritas hidrofóbicas se refieren a tubos de filtración vendidos por Whatman.

Cromatografía de capa preparativa se refiere al uso de placas TLC vendidas por Merck recubiertas con gel de sílice 60 F_{254}.

Intermedio 1

1- [2- (metilsulfonil) fenil]metanamina



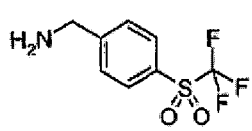
A una solución vigorosamente agitada de 1- [2- (metilito) fenil]metanamina (5g) en diclorometano (250 ml) a 5°C se agregó el ácido m- cloroperoxibenzoico (22.7 g) por porciones. La reacción se agitó a 0°C durante 30 min, luego a 20°C durante 18 horas. La reacción se cargó en cartuchos SCX- SPE 3x20g, se lavó con metanol y eluyó en 2M amoniaco/metanol. La concentración del último proporcionó el producto como un aceite amarillo (3.9g, 64%) .

LCMS (A) Rt = 0.38 min; m/z $[M+H]^+$ = 186

^1H NMR ($CDCl_3$) δ 8.13 (d, 1H) , 7.65 (t, 1H) , 7.54 (d, 1H) , 7.44 (t, 1H) , 4.27 (s, 2H) , 3.22 (s, 3H) , 1.68 (br s, 2.5H (incluye agua)) .

Intermedio 2

1- {4- [(Trifluorometil) sulfonil]fenil}metanamina.



A 4- [(trifluorometil) sulfonil]benzonitrilo (1.6g) en THF (20mL) a 20°C se agregó complejo de borano- tetrahidrofurano (1.0M, 13.4mL) por canula. La mezcla se agitó durante 1 hora antes de calentar a reflujo durante 18 horas, se enfrió a 0°C luego se apago con metanol (5 mL) . La

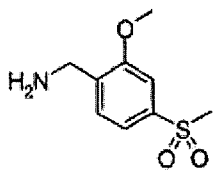
mezcla se calentó a 70°C, y luego se enfrió y el solvente se retiró al vacío. El residuo resultante se disolvió en metanol y se pasó a través de un cartucho SCX- SPE de 20 g. El cartucho se lavó con metanol y la amina de producto eluyó con 2.0M amoniaco/metanol. El retiro del solvente al vacío proporcionó la amina como un aceite amarillo (1.4g, 89%) .

LCMS (A) RT = 1.66 minutos; m/z $[M+H]^+$ = 240

1H NMR (CDCl3) δ 7.98 (d, 2H) , 7.68 (d, 2H) , 4.09 (s, 2H) .

Intermedio 3

Hidrocloruro de {[2- (Metoxi) - 4- (metilsulfonil) fenil]metil}amina.



A una solución de ácido 2- (metoxi) - 4- (metilito) benzoico (4.0 g) en éter dietílico (10 mL) a 0 °C se agregó una solución de hidruro de aluminio y litio en éter etílico (1.0M, 30 mL) , La mezcla se agitó a 20 °C durante 3 días y se apagó con agua (1.2 mL) , NaOH acuoso (15%, 1.2 mL) y agua (3.4 mL) . Se agregó sulfato de sodio (anhidro, 2g) y la mezcla se agitó durante 5 minutos en donde el sólido se removió mediante filtración, se lavó con éter y el filtrado se redujo al vacío. Una porción del residuo (0.9 g) se disolvió en cloroformo (10 mL) y diisopropiletilamina (1.1 mL) y se agregó sulfonilcloruro de metano (0.46 mL) regulando la temperatura bajo 35 °C. La mezcla se agitó durante 48 horas, se agregó agua (5 mL) , la capa acuosa se extrajo con cloroformo (2x5 mL) y los orgánicos combinados se redujeron al vacío. El residuo resultante se disolvió en dimetilformamida (3 mL) y se agregó a una mezcla de imidodicarbonato de bis(1,1-dimetiletil) (1.3 g) y tert- butoxido de potasio (0.67 g) en dimetilformamida (12 mL) . La mezcla se calentó a 100 °C durante 3 horas, se enfrió a 0°C y se apagó con cloruro de amonio saturado (15 mL) . La mezcla resultante se redujo mediante ca. 80% al vacío y agua (50 mL) y se agregó acetato de etilo (100 mL) . La capa sobrenadante se lavó con agua (2 x 50 mL) y salmuera saturada (50 mL) y se secó sobre sulfato de sodio antes de ser reducida al vacío. La cromatografía de columna de sílice (acetato de etilo/ciclohexano) del residuo proporcionó el imido- carbonato (2.2 g) , 049 g el cual luego se disolvió en diclorometano (7 mL) y agua (6 mL) y se agregó carbonato de hidrogeno de sodio (0.49 g) y ácido 3- cloroeroxibenzoico (1.5 g) . La

mezcla se agitó durante 24 horas y la mezcla se particionó entre carbonato de hidrogeno de sodio (10 mL) y cloroformo (10 mL) . Los orgánicos combinados se redujeron al vacío y el residuo se purificó mediante cromatografía de columna de sílice (acetato de etilo/ciclohexano) . Luego la sulfona resultante (0.35 g) se disolvió en metanol/diclorometano (4:1, 10 mL) y se agregó cloruro de acetilo (0.35 mL) a 0 °C. La mezcla se agitó durante 24 horas y se redujo al vacío para proporcionar el compuesto del título (210 mg) .

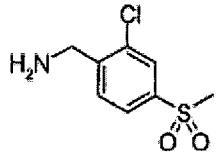
LCMS(A) Rt = 0.38 minutos; m/z $[M+H]^+ = 216$

^1H NMR ($CDCl_3$) δ 8.41 (br s, 3H) , 7.68 (d, 1H) , 7.56 (d, 1H) , 7.50 (s, 1H) , 4.08, (br q, 3H) , 3.95 (s, 3H) , 3.931 (s, 3H) .

Antes de la inclusión en la reacción Ugi la base libre de la amina se obtuvo mediante un cartucho de aminopropil- SPE o mediante un tratamiento con un equivalente de trietilamina.

Intermedio 4

Hidrocloruro de {[2- cloro- 4- (metilsulfonil) fenil]metil}- amina.



A una solución de ácido 2- cloro- 4- (metilsulfonil) benzoico (4.5 g) en éter etílico (1.0M, 30 mL) a 0°C se agregó una solución de hidruro de aluminio y litio en éter etílico (1.0M, 30mL) . La mezcla se agitó a 20°C durante 3 días y se apago con agua (1.2 mL) , NaOH acuoso (15%, 1.2mL) y agua (3.4 mL) . Se agregó sulfato de sodio (anhidro, 2g) y la mezcla se agitó durante 5 minutos después de lo cual el sólido se removio mediante filtración, se lavó con éter y el filtrado se redujo al vacío. El residuo (2.8 g) se disolvió en tetrahidrofurano (10 mL) y diisopropiletilamina (2.7 mL) y se agregó sulfonilcloruro de metano (1.2 mL) regulando la temperatura bajo 35 °C. La mezcla se agitó durante 48 horas, se agregó agua (5 mL) , la capa acuosa se extrajo con cloroformo (2 x 5 mL) y los orgánicos combinados se redujeron al vacío. El residuo resultante se disolvió en dimetilformamida (10 mL) y se agregó a una mezcla de imidodicarbonato (3.4 g) y Pert- butoxido de potasio (1.8 g) en dimetilformamida (30 mL) . La mezcla se calentó a 100 °C durante 2 horas, se enfrió a 0 °C y se apagó con cloruro de amonio saturado(30 mL) . La mezcla resultante se redujo mediante ca. 80% al vacío y agua (100 mL) y

se agregó acetato de etilo (200 mL) . La capa sobrenadante se lavó con agua (2 x 50 mL) y salmuera saturada (50 mL) y se secó sobre sulfato de sodio antes de ser reducida al vacío. La cromatografía de columna de sílice (acetato de etilo/ciclohexano) del residuo proporcionó el imido- carbonato (2.3 g) el cual fue luego disuelto en metanol/diclorometano (4:1, 10 mL) y se agregó cloruro de acetilo (0.35 mL) a 0 °C. Luego la mezcla se agitó durante 24 horas y se redujo al vacío para proporcionar el compuesto de el título.

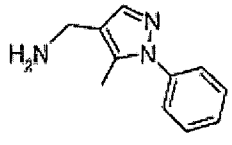
LCMS(A) Rt = 0.3 minutos; m/z $[M+H]^+$ = 220

^1H NMR ($CDCl_3$) δ 8.76 (br s., 3H) , 8.10 (s, 1H) , 7.97 (d, 1H) , 7.87 (d, 1H) , 4.23 (s, 2H) , 3.34 (s, 3H) .

Antes de la inclusión en la reacción Ugi la base libre de la amina se obtuvo mediante un cartucho de aminopropil- SPE o mediante un tratamiento con un equivalente de trietilamina.

Intermedio 5

[(5- Metil- 1- fenil- 1H- pirazol- 4- il) metil]amina.



Una solución de 5- metil- 1- fenil- 1h- pirazolo- 4- carboxilato de etilo (1 g, 4.3 mmol) en éter seco (4 ml) bajo N_2 se enfrió a - 75 °C. Se agregó hidruro de aluminio y diisobutilo (1M en hexano, 8.6 ml) durante 10 minutos y la reacción se agitó a - 70 °C durante 2 horas. Luego se agregó metanol seco (0.85 ml) y la reacción se dejo enfriar durante una hora adicional. Se agregó ácido clorhídrico (2M, 4.5 ml) y la reacción se dejo calentar a temperatura ambiente y se agitó durante 20 minutos La fase orgánica se separó y la fase acuosa se extrajo con diclorometano (2 x 50 ml) . Los orgánicos combinados se secaron y se concentraron para proporcionar (5- metil- 1- fenil- 1H- pirazol- 4- il) metanol como un sólido amarillo pálido (816 mgs, 100%) .

LCMS (A) Rt = 2.15 minutos; m/z $[M+H]^+$ =189

Se agregó perrutenato de tetrapropilamonio (76 mg) a una mezcla de (5- metil- 1- fenil- 1H- pirazol- 4- il) metanol (816 mg, 4,3 mmol) , N- oxido de 4- metilmorfolina (754 mg, 6.45 mmol) y tamices moleculares (4 A) en diclorometano seco (12.6 ml) . La reacción se agitó durante 40 minutos y luego se filtró a través de un tapón de sílice lavando con diclorometano. La

concentración proporcionó 5- metil- 1- fenil- 1H- pirazolo- 4- carbaldehido como un sólido amarillo pálido (763 mg, 95%) .

LCMS (A) Rt = 2.39 minutos; m/z $[M+H]^+$ =187

Se disolvió 5- metil- 1- fenil- 1H- pirazolo- 4- carbaldehido (763 mg, 4.1 mmol) en etanol (3 ml) y piridina (3 ml) y se agregó hidrocloruro de hidroxilamina. (441 mg, 4.8 mmol) . La mezcla se calentó a reflujo durante 2 horas. La reacción se dejo enfriar a temperatura ambiente y se particionó entre agua y cloroformo (2 x 20 ml) . La fase orgánica se secó (Na_2SO_4) y se concentro para proporcionar oxima de 5- metil- 1- fenil- 1H- pirazolo- 4- carbaldehido como una mezcla de isómeros, sólido amarillo pálido, (856 mg) .

LCMS (A) Rt = 2.38 minutos; m/z $[M+H]^+$ =202

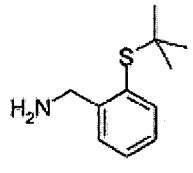
A una solución de oxima de 5- metil- 1- fenil- 1H- pirazolo- 4- carbaldehido (588 mg, 2.93 mmol) en tetrahidrofurano (4.8 ml) a 0 °C se agregó hidruro de aluminio de litio (solución 1 M en tetrahidrofurano, 4.4 ml) . La reacción se agito por una hora y luego se calentó a reflujo durante 18 horas. La reacción se enfrió a 0 °C y se apagó mediante la adición de agua (0.167 ml) , hidróxido de sodio 15% (0.167 ml) y agua (0.5 ml) . Luego se agrego Na_2SO_4 (0.33 g) . La reacción se filtró y el filtrado se concentró para proporcionar [(5- metil- 1- fenil- 1H- pirazol- 4- il) metil]amina como aceite amarillo (615 mg, 112% contiene algún tetrahidrofurano) .

LCMS (A) Rt = 1.62 minutos; m/z $[M+H]^+$ =188

^1H NMR ($CDCl_3$) δ 7.61 (s, 1H) 7.5- 7.37 (m, 5H) , 3.75 (s, 2H) , 2.32 (s, 3H) , 1.67 (s, 2H) .

Intermedio 6

({2- [(1,1- Dimetiletiltio]fenil}metil) amina

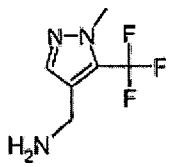


Preparado de manera similar a [(5- metil- 1- fenil- 1H- pirazol- 4- il) metil]amina (Intermedio 5) a partir de 2- [(1,1- dimetiletil) tio]benzaldehido comercialmente disponible.

^1H NMR ($CDCl_3$) δ 7.55 (dd, 1H) , 7.41 (dd, 1H) , 7.35 (dt, 1H) , 7.23 (dt, 1H) , 4.07 (s, 2H) , 1.57 (br s, 2H) , 1.31 (s, 9H.

Intermedio 7

{[1- Metil- 5- (trifluorometil) - 1H- pirazol- 4- il]metil}amina



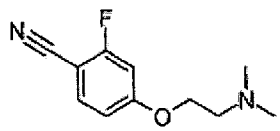
Preparado de manera similar a [(5- metil- 1- fenil- 1H- pirazol- 4- il) metil]amina (Intermedio 5) a partir de 1- metil- 5- (trifluorometil) - 1H- pirazolo- 4- carboxilato de etilo comercialmente disponible.

LCMS (A) Rt = 0.42 minutos; m/z $[M+H]^+$ =180

^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H) , 3.92 (s, 3H) , 3.83 (s, 2H) , 1.56 (br s, 2H) .

Intermedio 8

4- {[2- (Dimetilamino) etil]oxi}- 2- fluorobenzonitrilo

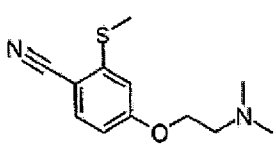


Se agregó una solución 1.0M de t- butoxido de potasio en tetrahidrofurano (7 mL) lentamente a una solución de N,N- dimetiletanolamina (0.75 mL, 7- 19 mmol) en tetrahidrofurano (5 mL) a 0- 5 °C y la solución se agitó durante 30 minutos. La mezcla se agregó a una solución de 2,4- difluorobenzonitrilo (1.00 g, 7.19 mmol) en THF (5 mL) a - 65 °C y la mezcla resultante se agitó a - 65 °C durante 3 horas, luego se dejo calentar a temperatura ambiente y se agitó durante la noche. Luego la mezcla se enfrió a 5 °C y se apagó con agua (40 mL) , luego se diluyó con éter dietílico (150 ml) . La fase orgánica se lavó con agua (50 mL) , luego con salmuera (50 mL) , se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida para proprcionar el compuesto del título como un aceite amarillo (83%) .

^{1}H NMR ($CDCl_3$) δ 7.47 (m, 1H) , 6.65 (m, 2H) ,4.09 (t, 2H) ,2.74 (t, 2H) , 2.30 (s, 6H)

Intermedio 9

4- {[2- (Dimetilamino) etil]oxi}- 2- (metiltio) benzonitrilo



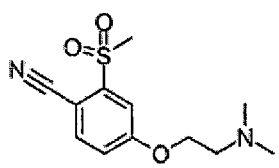
Se disolvió metanetiolato de sodio (0.46 g) en THF seco (30 mL) ; esta solución se trató con una solución de 4- {[2- (dimetilamino) etil]oxi}- 2- fluorobenzonitrilo (1.25 g) (Intermedio 8) en THF seco (40 mL) agregado durante 90 minutos. La mezcla se agitó a temperatura ambiente durante la noche. Luego se trató con cloruro de amonio acuoso (17 mL) seguido después de 10 minutos por carbonato de hidrogeno de sodio acuoso (40 mL) . La fase acuosa se extrajo con diclorometano (DCM) y la fase orgánica se lavó con carbonato de hidrogeno de sodio acuoso, luego con salmuera, se secó sobre sulfato de sodio anhidro, luego se concentró bajo presión reducida para proporcionar una mezcla ca. 2:1 de 4- {[2- (dimetilamino) etil]oxi]}- 2- fluorobenzonitrilo y 4- [{2- (dimetilamino) etil]oxi}- 2- (metilito) benzonitrilo (1.65 g) . Esta se disolvió en DMF seco (5 mL) y se agregó a una solución de metanetiolato de sodio (0.72 g) en DMF seco bajo nitrogeno durante 1 hora. Esta mezcla se agito a temperatura ambiente durante la noche, luego se apagó con cloruro de amonio acuoso (30 mL) y carbonato de hidrogeno de sodio acuoso (50 mL) . La fase acuosa se extrajo con DMC y la fase orgánica se lavó con carbonato de hidrógeno de sodio acuoso; luego con salmuera, se secó sobre sulfato de sodio anhidro, luego se concentró bajo presión reducida para proporcionar el compuesto del título como un aceite amarillo (57%) .

LCMS (A) Rt = 1.82 minutos; m/z $[M+H]^+$ =237

^1H NMR ($CDCl_3$) δ 7.43 (d, 1H) , 6.82- 6.77 (m, 2H) , 4.17 (t, 2H) , 2.82 (t, 2H) , 2.51 (s, 3H) , 2.37 (s, 6H)

Intermedio 10

4- {[2- (Dimetilamino) etil]oxi}- 2- (metilsulfonil) benzonitrilo



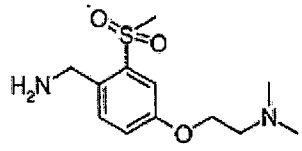
Se disolvió 4- {[2- (Dimetilamino) etil]oxi}- 2- (metiltio) benzonitrilo (Intermedio 9) (1.06 g) en DMC seco (10 mL) bajo nitrógeno y la solución se trató con mCPBA (3.35 g) . La mezcla resultante se agitó durante la noche. Se agregó DCM (100 mL) seguido por agua (20 mL) . La fase acuosa se saturó con sulfito de sodio y carbonato de sodio; luego la mezcla se agitó durante 30 minutos y las fases se separaron. La fase acuosa se lavó con DMC (x3) y la fase orgánica se

lavó con carbonato de sodio acuoso saturado. Los extractos orgánicos se concentraron bajo presión reducida para proporcionar el compuesto del título como un aceite (47%) .

^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1H) ,7.56- 7.49 (m, 2H) , 4.26 (s amplio, 2H) , 34.05 (s, 3H) , 2.83 (s amplio, 2H) , 2.35 (s amplio, 6H)

Intermedio 11

1- {[4- (Aminometil) - 3- (metilsulfonil) fenil]oxi}- N,N- dimetiletanamina

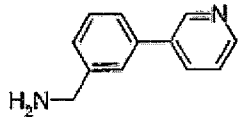


Una solución de 4- {[2- (Dimetilamino) etil]oxi}- 2- (metilsulfonil) benzonitrilo (Intermedio 10) (0.52 g) en ácido acético glacial (40 mL) fue hidrogenada sobre 10% paladio sobre carbón de leña (0.4 g) a 1 atmósfera de hidrógeno durante 3 horas. Después de purgar el sistema con nitrógeno, el catalizador se removió mediante filtración bajo nitrógeno y se lavó con un pequeño volumen de DMC. Los filtrados combinados se concentraron bajo presión reducida para proporcionar el producto crudo como un aceite amarillo; este se disolvió en ácido clorhídrico 2M y la solución se concentro bajo presión reducida, luego se disolvió en una mezcla de metanol y tolueno y esta solución se concentro bajo presión reducida para proporcionar el dihidrocloruro del compuesto del título. Este se convirtió en la base libre utilizando un cartucho de aminopropilo SPE de 10 g eluido con etanol. Las fracciones conteniendo el producto se combinaron y evaporaron bajo presión reducida para proporcionar el compuesto del título como un aceite amarillo (80%) .

^{1}H NMR ($CDCl_3$) δ 7.37 (m, 2H) , 7.27 (s, 1H) , 4.06 (t, 2H) , 3.78 (s, 2H) , 2.94 (s, 3H) , 2.67 (t, 2H) , 2.22 (s, 6H)

Intermedio 12

1- [3- (3- Piridinil) fenil]metanamina



Una mezcla de 3- bromopiridina (0.12 ml, 1.2 mmol) , ácido [3- (aminometil) fenil] borónico (568 mg, 3.2 mmol) y tetrakis(trifenilfosfina) paladio(0) (39 mg, 0.033 mmol) en carbonato de

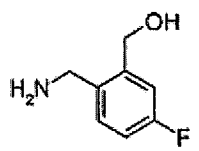
sodio acuoso (1M, 4 ml) y dimetoxietano (8 ml) se calentó a reflujo durante 3 horas y luego se enfrió. La mezcla se trató con 50 ml de agua y se extrajo con 3 x 30 ml de diclorometano. La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y evaporó para revelar un aceite amarillo. El producto se purificó mediante cromatografía utilizando un cartucho SPE Bond Elute de 5g y eluyendo con una mezcla de diclorometano, etanol y amoniaco acuoso (200:8:1) para proporcionar 100 mg (45%) del compuesto del título como un aceite incoloro.

LCMS MH+ 185.

^{1}H NMR (400Mhz, $CDCl_3$) δ 3.97 (s, 2H) , 7.34- 7.38 (m, 2H) , 7.45- 7.48 (m, 2H) , 7.54 (bs, 1H) , 7.87- 7.91 (m, 1H) , 8.58- 8.61 (m, 1H) , 8.84- 8.87 (m, 1H) .

Intermedio 13

[2- (Aminometil) - 5- fluorofenil]metanol



A una solución de 2- bromo- 4- fluorobenzonitrilo (5 g, 25 mmol) en tetrahidrofurano (17 ml) a –30 °C se agregó cloruro de isopropilmagnesio (2M en tetrahidrifurano, 15 ml, 30 mmol y la reacción se agitó durante 3 horas. Luego se agregó dimetilformamida (5.79 ml, 75 mmol) y la reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. Luego la reacción se enfrió a –10 °C y se agregó ácido clorhídrico (2M, 37 ml) y la reacción se agitó durante 20 minutos. Luego la reacción se redujo a ~1/3 del volumen original y se particionó con acetato de etílo Luego los orgánicos se secaron y se concentraron para proporcionar 4- fluoro- 2- formilbenzonitrilo como un sólido marrón, 2,78 g.

^{1}H NMR ($CDCl_3$, 400 Mhz) : δ (ppm) =10.35 (1H, s) ; 7.9- 7.86 (1H, m) ;7.75 (1H, dd, J= 8.16, 2.64 Hz) , 7.49- 7.44 (1H, m) .

LCMS: Tiempo de reteción 2.25, no se observó ES^+.

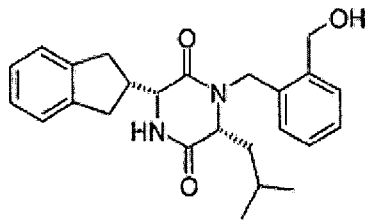
A una solución de 4- fluoro- 2- formilbenzonitrilo (2.78 g, 18.6 mmol) en tetrahidrofuran anhidro (34 ml) a 0 °C se agregó aluminiohidruro de litio (1M en tetrahidrofurano, 37.2 ml) y la reacción se agitó durante 1 hora. Se agregó agua (1.14 ml) , hidroxido de sodio al 15% (1.14 ml) y agua (3.42 ml) de manera secuencial seguido por la adición de sulfato de sodio (1.4 g) . Luego

la reacción se filtró y concentró para proporcionar [2- (aminometil) - 5- fluorofenil]metanol como un aceite marrón, 2.8 g.

^{1}H NMR ($CDCl_3$, 400 Mhz) : δ (ppm) = 7.24- 7.20 (1H, m) ; 7.11- 7.08 (1H, m) ; 6.97- 6.92 (1H, m) ; 4.6 (2H, m) ; 4.0 (2H, m) .

Intermedio 14

(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 1- {[2- (hidroximetil) - fenil]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona



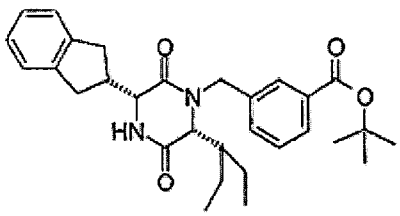
Se disolvió [2- (Aminometil) fenil]metanol (3.509 g, 25.58 mmol) en metanol (25 ml) y se agregó 3- metilbutanal (2.75 ml, 25.63 mmol) seguido por ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}amino) etanóico (7.453 g , 25.58 mmol) . La mezcla se agitó durante 15 minutos antes de agregar isocianuro de 2- [(fenilmetil) oxi]fenilo (5.35 g, 25.58 mmol) . La mezcla se agitó durante 1.3 horas y luego se dejó sentar a temperatura ambiente durante 7 noches antes de enfriarse en un baño de hielo/agua. Luego se agregó cloruro de acetilo (10.9 ml, 153.4 mmol) . Luego la mezcla se agitó en el baño de enfriamiento durante 10 minutos adicionales antes de ser agitada a temperatura ambiente. Después de 4.25 horas la mezcla se evaporó bajo presión reducida para dejar una espuma marrón oscura. Luego la espuma se agitó en cloroformo (50 ml) y solución de bicarbonato de sodio acuoso saturado (40 ml) durante 60 minutos antes de diluir con cloroformo (100 ml) y se separaron las fases. La fase acuosa se extrajo con cloroformo (3 x 50 ml) . La fase orgánica combinada se secó ($MgSO_4$) y concentró bajo presión reducida a 80 ml aproximadamente. La solución de cloroformo se trató con ácido acético glacial (2 ml) y se dejo sentar a temperatura ambiente durante 5 noches. Luego la mezcla de reacción se lavó con ácido clorhídrico 2M (70 m) , se diluyó con cloroformo y se filtró. La fase orgánica filtrada se lavó con solución de bicarbonato de sodio acuoso saturado (70 ml) . La fase orgánica se lavó ($MgSO_4$) , se evaporó bajo presión reducida y se secó al vacío para dejar un sólido marrón oscuro. El sólido se cargó en diclorometano sobre una columna de cromatografía de sílice rápida de 330 g (pre- eluida con acetato de etilo al 20% en ciclohexano) . La columna

fue eluida con acetado de etilo del 20% al 100% en ciclohexano para proporcionar (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (hidroximetil) - fenil]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona (1.563 g) como una espuma marrón pálido.

LCMS (A) Rt = 3.17 minutos; m/z $[M+H]^+$ =407.

Intermedio 15

3- {[(3R,6R) - 3- (2,3- dihidro- 1H- imden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoato de 1,1- Dimetiletilo



Se disovió 1,1- Dimetiletil- 3- (aminometil) benzoato (2.69 g, 12.98 mmol) en metanol (15 ml) y se agregó 2- etilbutanal (1.6 ml, 13 mmol) seguido por ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(fenilmetil) oxi]carbonil}amino) etanóico (4.225 g, 12.99 mmol) . La mezcla se agitó durante 11 minutos antes de agregar isocianuro de 2- [(fenilmetil) oxi]fenilo (2.73 g, 13 mmol) . La mezcla se agitó a temperatura ambiente durante 1.8 horas y luego se dejo sentar durante el fin de semana (65 horas) antes de evaporar el solvente bajo presión reducida para dejar una espuma arenosa. La espuma en solución en etanol (90 ml) conteniendo ácido acético (1.5 ml) se hidrogenó a temperatura ambiente y presión sobre 10% Pd/carbono (1.42) durante 18.5 horas. La reacción se filtró a través de filtros de fibra de vidrio y el solvente se removio al vacío para proporcionar una espuma marrón pálido. La espuma se agitó en cloroformo (50 ml) y se trató con ácido acético (2 ml) . La mezcla se agitó durante la noche (21.5 horas) a temperatura ambiente. Luego la mezcla de reacción se agitó con cloroformo (100 ml) y se lavó con ácido clorhídrico 2M (40 ml) seguido por solución de bicarbonato de sodio acuoso saturado (40 ml) . Las fases se separaron mediante una frita hidrofóbica y la fase orgánica se evaporó bajo presión reducida y se secó al vacío para dejar un sólido marrón. El sólido se cargo en diclorometano sobre una columna de cromatografía de sílice rápida de 120 g (pre- eluida con acetato de etilo al 10% en ciclohexano) . La columna se eluyó con 10% al 100% acetato de etilo en ciclohexano para proporcionar 3- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5-

dioxo- 1- piperazinil]metil}benzoato de 1,1- dimetiletil como un sólido amarillo pálido (2.115 g)

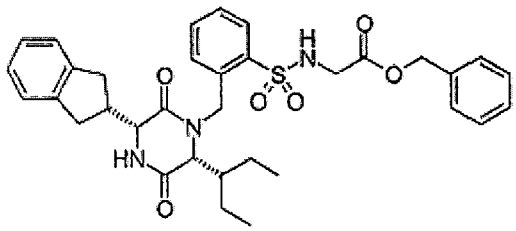
225

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LCMS (A) Rt = 3.77 minutos; m/z $[M+H]^+$ =508

Intermedio 16

N- [(2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) sulfonil]glicinato de fenilmetilo

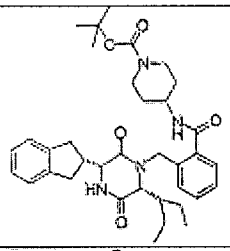
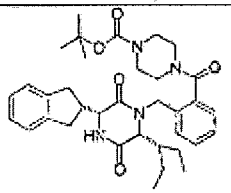


A una solución de cloruro de 2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzenosulfonilo (Intermedio 20) (100 mg) en diclorometano (2 ml) se agregó diisopropiletilamina (78 ul) y hidrocloruro de glicinato de fenilmetilo (39 mg) y la mezcla se agitó durante 3 horas a 20 °C. Se agregó metanol (2 ml) y la mezcla se pasó a través de un columna de aminopropil- SPE de 2 g y el solvente se removio. El residuo resultante se purificó utlizando una columna de Si- SPE de 2 g eluyendo con acetato de etilo/ciclohexato (40-50%) para proporcionar el compuesto del título (69 mg) como un aceite.

LCMS (A) Rt = 3.67 minutos; m/z $[M+H]^+$ = 618,$[M]^-$ =616

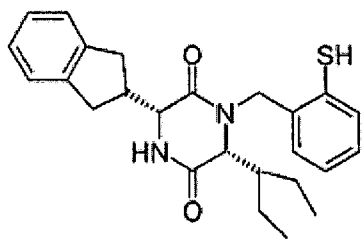
Intermedios 17- 18 se prepararon mediante métodos analogos a aquel descrito para el Ejemplo 66 a partir de ácido 2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico. (Ejemplo 65)

Int. No.	Estructura	Mwt	Rt/ min	+ve ; - ve	Nombre

17		616.8	3.48 (A)	617; 615	4. {[(2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) carbinil}- 1- piperidinacarboxilato de 1,1- dimetiletilo
18		602.7	3.62 (A)	603; 601	4. [(2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) carbinil]- 1- piperazina- carboxilato de 1,1- dimetiletilo

Intermedio 19

(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- mercaptofenil) - metil]- 2,5- piperazinadiona



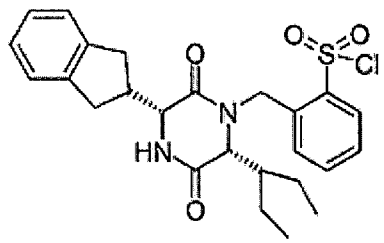
A una solución de (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(1,1- dimetiletil) tio]- fenil}metil) - 6- 1- etilpropil) - 2,5- piperazinadiona (Ejemplo 60) (8.0 g) en ácido acético (80 mL) se agregó cloruro 2- nitrobencenosulfenilo (3.3 g) y la mezcla se agitó a 20 °C durante 24 horas. El ácido acético se redujo al vacío, el residuo amarillo resultante se disolvió en dimetilformamida (36 mL) y la mezcla se degasificó mediante una corriente de gas nitrógeno durante 20 minutos. Luego se agregó trietilamina (3.3 mL) e hidrocloruro de tris(carboxietil) fosfina (6.7 g) y la mezcla se agitó a 20 °C durante 1.5 horas bajo gas de nitrógeno. La mezcla se redujo al vacío mediante ca. al 50% después de lo cual se agregó acetato de etilo (400 mL) y la mezcla se lavó con agua degasificada (2 x 250 mL) , salmuera (200 mL) y se secó sobre sulfato de sodio. El retiramiento del solvente al vacío y cromatografía de columna de sílice (acetato de etilo/ciclohexano) proporcionó el compuesto del título (5.8 g, 82%) .

LCMS (A) Rt = 3.7 minutos; m/z $[M+H]^+$ =423

^{1}H NMR δ 7.15- 7.35 (m, 8H) , 7.01 (br d, 1H) , 5.33 (d, 1H) , 4.23 (d, 1H) , 4.15 (dd, 1H) , 3.52 (br s, 1H) , 3.18 (m, 3H) , 2.97 (m, 1H) , 2.82 (dd, 1H) , 1.52- 1.80 (m, 4H) , 1.32 (m, 1H) , 0.92 (m, 6H) .

Intermedio 20

Cloruro de 2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benzenosulfonilo



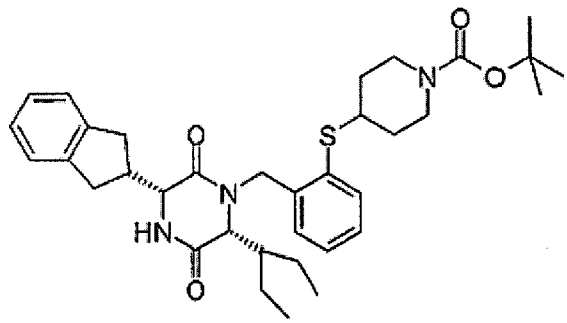
A una solución de (3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- mercaptofenil) - metil]- 2,5- piperazinadiona (Intermedio 19) (2.4 g) en acetonitrilo (60 ml) a 0 °C se agregó nitrato de potasio (1.7 g) seguido por una adición por goteo de cloruro de sulfurilo (1.4 ml) . La mezcla se agitó a 0- 10 °C durante 2.5 horas. Se disolvió carbonato de sodio (4 g) en agua (100 ml) y se agregó a la reacción a 0 °C, la mezcla se agitó durante 2 minutos y se particionó entre acetato de etilo (200 ml) y agua (50 ml) . La capa acuosa se extrajo con acetato de etilo (2 x 50 ml) y los orgánicos combinados se lavaron con salmuera saturada (150 ml) y se secaron sobre sulfato de magnesio. El retiro del solvente al vacío y cromatografía de columna de sílice (diclorometano, cloroformo, éter dietílico y acetato de etilo) proporcionó el compuesto del título (1.5 g, 54%) .

LCMS (A) Rt = 3.7 minutos; m/z $[M+H]^+$ = 489

^{1}H NMR δ 8.14 (d, 1H) , 7.70 (t, 1H) , 7.55 (t, 1H) , 7.31 (d, 1H) , 7.2 (m, 5H) , 5.43 (d, 1H) , 5.04 (d, 1H) , 4.20 (dd, 1H) , 4.11 (d, 1H) , 3.20 (m, 3H) , 3.06 (m, 1H) , 2.88 (dd, 1H) , 1.68 (m, 4H) , 1.38 (m, 1H) , 0.95 (t, 3H) , 0.87 (t, 3H) .

Intermedio 21

4- [(2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) tio]- 1- piperidinecarboxilato de 1,1- dimetiletilo



A una solución de (3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- mercaptofenil) - metil]- 2,5- piperazinadiona (Intermedio 19) (800 mg) en acetonitrilo (3.2 ml) se agregó 4- [(metilsulfonil) oxi] de 1,1- dimetiletilo (477 mg) . La reacción se enfrió a 0 °C y se degasificó con una corriente de gas nitrógeno durante 20 minutos.

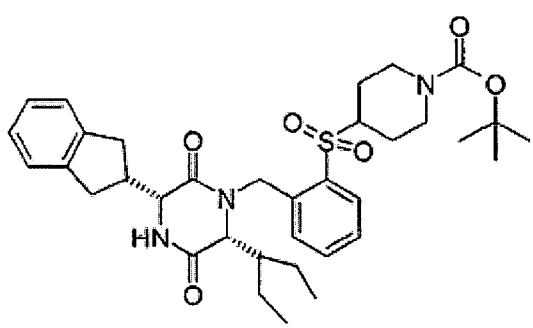
Se agregó carbonato de potasio (330 mg) y la reacción se calentó a 80 °C durante 3 horas. La reacción se particionó entre agua (12 ml) y acetato de etilo (12 ml) y la capa acuosa se extrajo con acetato de etilo (23 x 12 ml) . Los orgánicos combinados se concentraron y el residuo se purificó mediante cromatografía de columna de sílice (acetato de etilo/ciclohexano) para proporcionar el compuesto del título (670 mg, 65%) .

LCMS (A) Rt = 4.0 minutos; m/z $[M+H]^+$ = 606

^{1}H NMR δ 7.48 (m, 1H) , 7.20 (m, 7H) , 6.52 (br d, 1H) , 5.28 (d, 1H) , 4.51 (d, 1H) , 4.13 (m, 1H) , 3.97 (m, 3H) , 3.17 (m, 4H) , 2.80- 3.00 (m, 4H) , 1.92 (br d, 2H) , 1.62 (m, 5H) , 1.48 (s, 9H) , 1.29 (m, 1H) , 0.88 (m, 1H) .

Intermedio 22

4- [(2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) sulfonil]- 1- piperidinecarboxilato de 1,1- dimetil



A una solución de 4- [(2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) tio]- 1- piperidinecarboxilato de 1,1- dimetiletilo (Intermedio

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21) (670 mg) en diclorometano (7.4 ml) se agregó ácido 3- cloroperoxibenzóico (570 mg) y la mezcla se agitó durante 2 horas. La mezcla se apagó mediante adición por goteo de solución de sulfito de sodio al 10% (5 ml) y la mezcla se agitó durante 5 minutos. La capa orgánica se separó y la fase acuosa se lavó con diclorometano (2 x 5 ml) y los orgánicos combinados se redujeron al vacío. El residuo se disolvió en metanol y se purificó mediante aminopropil- SPE, eluyendo el producto en metanol. La evaporación al vacío proporciono el compuesto del título (690 mg, 98%)

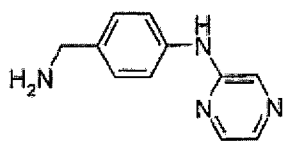
.

LCMS (A) Rt = 3.7 minutos; m/z $[M+H]^+$= 638

^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H) , 7.57 (t, 1H) , 7.46 (t, 1H) , 7.28 (d, 1H) , 7.2 (m, 4H) , 6.5 (br d, 1H) , 5.32 (d, 1H) , 4.80 (d, 1H) , 4.25 (br m, 2H) , 4.11 (m, 2H) , 3.36 (br t, 1H) , 3.15 (m, 3H) , 2.98 (m, 1H) , 2.75 (br m, 3H) , 2.08 (br d, 1H) , 1.60- 1.80 m, 6H) , 1.53 (s, 9H) , 1.40 (m, 1H) , 1.03 (t, 3H) , 0.95 (t, 3H) .

Intermedio 23

4- (Pirazin- 2- il) aminobenzilamina

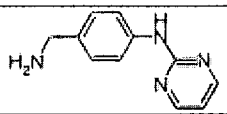
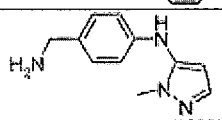


Una mezcla de 4- bromobenzonitrilo (3.76 g, 20.8 mmol) , aminopirazina (2.4 g, 25.3 mmol) , ligando xantfos (0.26, 0.45 mmol) , $Pd_2(dba)_3$ (0.255 g, 0.43 mmol) y carbonato de cesio (9.25 g,28.4 mmol) en dioxano 50 ml) se calentó a reflujo bajo nitrogeno durante 24 horas. La mezcla se enfrió, diluyó con THF, filtró, concentró al vacío, luego se cromatografió (sílice, acetato de etilo/éter de petroleo 1:3) para proporcionar 4- (pirazin- 2- il) aminobenzonitrilo crudo (2. 64 g) . Sin purificación adicional, este material (2.38 g) se hidrogenó en amoniaco metanólico (120 ml) sobre niquel Raney (0.36 g) a 50 psi durante 3 horas. El catalizador se filtró y la solución se evaporó para proporcionar 4- (pirazin- 2- il) aminobenzilamina (2.4 g) .

LCMS (A) Rt = 0.64 minutos; m/z $[M - NH_2]^+$ = 184

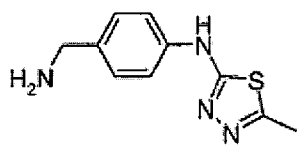
^{1}H NMR ($CDCl_3$) δ 8.21 (d, 1H) , 8.10 (m, 1H) , 7.96 (d, 1H) , 7.38 (d, 2H) , 7.30 (d, 2H) , 6.65 (br s, 1H) , 3.85 (s, 2H) .

Intermedios 24- 25 fueron preparados mediante métodos análogos a aquel descrito para el Intermedio 23.

Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
24		200.2	0.61	184	4- (pirimid- 2- il) aminobenzilamina
25		202.3	0.53 (c)	203	4- (1- metilimidazol- 2- il) amino- benzilanina

Intermedio 26

4- (5- Metil- 1,4,5- tiadiazol- 2- il) aminobenzilamina

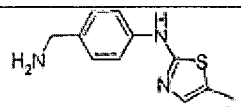


Se disolvió 5- Metil- 1,3,4- tiadiazol- 2- amina (19 g, 165 mmol) y tert- butóxido de potasio (24 g, 206 mmol) en DMSO (100 mL) y se agitó a temperatura ambiente durante 1 hora. Se agregó una solución de 4- fluorobenzonitrilo(10.8 g, 88.5 mmol) en DMSO (30 mL) por goteo durante 15 minutos. La reacción se calentó a 50 °C y se agitó durante 30 minutos. La mezcla de reacción se vertió en agua (1000 mL) y se formó un precipitado. La solución se ajustó a pH = 5 con 2N HCl (100 mL) y luego se filtró. El precipitado se disolvió en MeOH y se purificó mediante cromatografía rápida en gel de sílice para proporcionar 10.2 g de 4- [(5- metil) - 1,3,4- tiadiazol- 2- il) amino]benzonitrilo. Este material (2.2 g 10.2 mmol) se hidrogenó en amoniaco metanólico (125 mL) sobre niquel Raney (0.40 g, 6.8 mmol) a 50 psi durante 3 horas a temperatura ambiente. El catalizador se filtró y el filtrado se evaporó para proporcionar 1.9 g de N- [4- aminometil) fenil]- 5- metil- 1,3,4- tiadiazol- 2- amina.

^{1}H NMR (CD_3OD) δ 7.58 (d, 2H) , 7.37 (d, 2H) , 3.94 (s, 2H) , 2.59 (s, 3H)

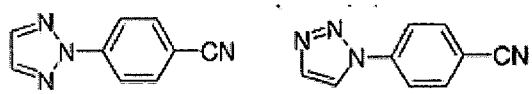
HPLC (C) Rt = 0.80 minutos; m/z $[M+H]^+$ = 221

Intermedio 27 se preparó mediante métodos analogos a aquel descrito para el Intermedio 23 excepto que se utilizó carbonato de sodio como la base.

Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
27		219.3	0.57	220	4- (5- metiltiazol- 2- il) amino- benzilamina

Intermedios 28 y 29

4- (2H- 1,2,3- Triazol- 2- il) benzonitrilo y 4- (1H- 1,2,3- triazol- 1- il) benzonitrilo



A una solución de 4- bromobenzonitrilo (10 g,54.9 mmol) en DMF seco (20 ml) se agregó sucesivamente 1H- 1,2,3- triazolo (3.81 g, 54.9 mmol) , yoduro de cobre(I) (0.5 g, 2.6 mmol) , (1S,2S) - N,N'- dimetil- 1,2- ciclohexanodiamina (1ml, 6.25 mmol) y carbonato de potasio (16 g, 116 mmol) . La mezcla se agitó bajo nitrogeno a 110 °C durante la noche. El solvente se evaporó al vacío, se agregó acetato de etilo al residuo y la solución resultante se fitró, secó y evaporó para proporcionar una mezcla de dos regioisomeros. La cromatografía proporcionó 4- (2H- 1,2,3- triazol- 2- il) benzonitrilo (Intermedio 28) (3.5 g)

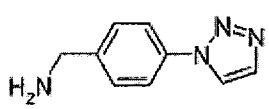
^{1}H NMR ($CDCl_3$) δ 7.79 (2H, d) , 7.88 (2H, s) , 8.23 (2H, d)

y 4- (1H- 1,2,3- trazol- 1- il) benzonitrilo (Intermedio 29) (2.3 g)

^{1}H NMR ($CDCl_3$) δ 7.84- 8.07 (6H, m)

Intermedio 30

{[4- (1H- 1,2,3- Triazol- 1- il) fenil]metil}amina



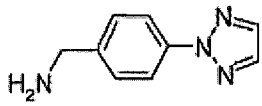
4- (1H- 1,2,3- trazol- 1- il) benzonitrilo (Intermedio 29) (2.3 g, 13.5 mmol) en THF (12 ml) se enfrió en hielo y se agregó hidruro de aluminio de litio (2.4 g, 63.2 mmol) por porciones. La mezcla se agitó a temperatura ambiente durante 1.5 horas, luego se recolectó en hielo y se agregó hidróxido de sodio acuoso (10 ml) por goteo. La solución resultante se filtró, y la capa de THF se secó y evaporó para obtener {[4- (1H- 1,2,3- trazol- 1- il) fenil]metil}amina (2.5 g)

LCMS (C) Rt = 0.45 minutos; m/z $[M+H]^+ = 175$

^1H NMR ($CDCl_3$) δ 3.96 (2H, s) , 7.49 (2H, d) , 7.71 (2H, d) , 7.84 (1H, delgado d) , 7.98 1H, delgado d) .

Intermedio 31

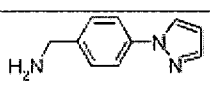
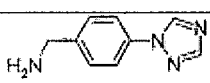
4- (1,2,3- Triazol- 2- il) benzilamina



Este compuesto se preparó a partir del Intermedio 28 mediante un método análogo a aquel descrito para el Intermedio 30.

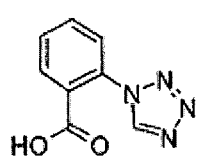
^1H NMR ($CDCl_3$) δ 3.92 (2H, s) , 7.43 (2H, s) , 7.79 (2H, s) , 8.03 (2H, d) .

Los Intermedio 32- 33 fueron preparados en dos pasos mediante métodos análogos a aquellos descritos para los Intermedios 29 y 30 excepto que en estos casos se obtuvo un único regioisómero

Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
32		173.2	0.66	157	4- (pirazol- 1- il) benzylamina
33		174.2	0.44	158	4- (1,2,4- triazol- 1- il) benzilamina

Intermedio 34

Ácido 2- (1H- Tetrazol- 1- il) benzóico



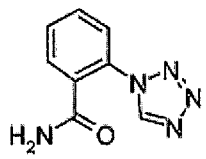
Una solución de ácido antranílico (10.0 g, 73 mmol) , azida de sodio (14.0 g, 217 mmol) y ortoformato de trimetilo (23.6 ml, 220 mmol) en ácido acético glacial (250 ml) se agitó a temperatura ambiente durante 2 horas. El sólido resultante se filtró y secó para obtener el producto deseado (8.73 g) .

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^{1}H NMR ($CDCl_3$) δ 7.46- 8.06 (3H, m) , 8.26 (1H, m) , 9.79 (1H, s)

Intermediado 35

2- (1H- Tetrazol- 1- il) benzamida

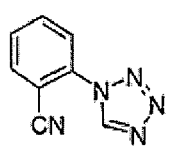


Una mezcla de ácido 2- (1H- tetrazol- 1- il) benzóico (Intermedio 34) (3.0 g) cloruro de amonio (1.68 g) , EDC.HCI (6.0 g) , diisopropiletilamina (10.8 ,l) y 1- hidroxi- 7- azabenzotriazola (4.2 g) en DMF (45 ml) se agitó a temperatura ambiente bajo argón durante 15 horas. Se agregó agua y la mezcla se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron y evaporaron para proporcionar el producto deseado (1.8 g) .

^{1}H NMR (CD_3OD) δ 7.63- 7.79 (4H, m) , 9.43 (1H, s)

Intermedio 36

2- (1H- Tetrazol- 1- il) benzonitrilo

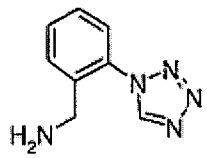


Se agregó trietilamina (0.4 ml) por goteo a una solución agitada de 2- (1H- tetrazol- 1- il) - benzamida (Intermedio 35 (110 mg) en oxicloruro de fosforo (10 ml) a temperatura ambiente. Luego de 30 minutos le mezcla se vertió en agua helada y se extrajo con acetato de etilo. El secado y la evaporacion de las capas orgánicas proporcionó el producto deseado (80 mg) .

^{1}H NMR ($CDCl_3$) δ 7.69- 7.94 (4H, m) , 9.26 (1H, s)

Intermedio 37

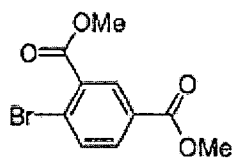
{[2- (1H- Tetrazol- 1- il) fenil]metil}amina



Una solución de 2- (1H- Tetrazol- 1- il) benzonitrilo (Intermedio 36) (120 mg) en amoniaco metanólico (20 ml) se hidrogenó sobre niquel Raney (0.5 g) a 40 psi durante 3 horas. El catalizador se fitró y la solución se evaporó para obtener el producto deseado (80 mg)
LCMS (C) Rt = 0.47 minutos; m/z $[M+H]^+$ =176

Intermedio 38

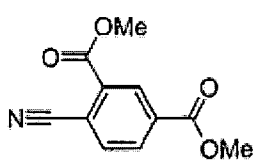
Éster dimetílico del ácido 4- bromoisoftálico



Una suspensión de ácido de 4- bromoisoftálico (10 g, 40.8 mmol) en MeOH (150 mL) se enfrió a 0 °C. Se agregó cloruro de tionilo (10 mL, 140 mmol) por goteo durante 10 minutos y la reacción se agitó a temperatura ambiente durante la noche. El solvente se removió. El sólido amarillo se retiro en 100 mL de diclorometano y se lavó con 30 mL de bicarbonato de sodio saturado. La fase orgánica se separó, se seco sobre $NaSO_4$ y concentró para proporcionar éster dimetílico de ácido 4- bromoisoftálico como un sólido blanco (11.0 g, 97%) .
LCMS (D) Rt = 2.60 minutos; m/z $[M+H]^+$ =273

Intermedio 39

4- ciano- 1,3- bencenodicarboxilato de dimetilo



Ester dimetílico del ácido 4- bromoisoftálico (Intermedio 38) (11 g, 40.3 mmol) , cianuro de cobre (I) (14.4 g, 16.12 mmol) , cianuro de tetraetil amonio (6.38 g, 40.3 mmol) , tris(dibencilideneactona) dipaladio (2.96 g, 3.2 mmol) , 1,1'- bis(difenilfosfino) - ferroceno (7.14

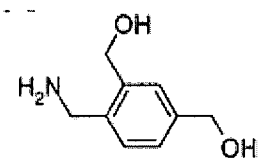
g, 12.9 mmol) y 100 mL de dioxano se mezclaron y sometieron a reflujo durante 2 horas bajo N_2. Luego la mezcla se enfrío a temperatura ambiente, se diluyó con 400 mL de acetato de etilo y se filtró a través de Celite. Luego el filtrado se lavó con 100 mL de bicarbonato de sodio saturado, se secó sobre $MgSO_4$ y se concentró. El material crudo se purificó mediante columna de gel de sílice combi flash eluyendo con 10- 50% acetato de etilo en hexanos para proporcionar 4- ciano- 1,3- bencenodicarboxilato de dimetilo como un sólido amarillo pálido (7.1 g,80.

LCMS (D) Rt = 2.23 minutos; m/z $[M+H]^+$ =220

^1H NMR ($CDCl_3$) δ 8.79 (s, 1H) , 8.32 (d, 1H) , 7.93 (d, 1H) , 4.06 (s, 3H) , 4.01 (s, 3H) .

Intermedio 40

[4- (Aminometil) benzeno- 1,2- diil]dimetanol



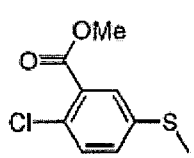
A una suspensión de hidruro de aluminio de litio (2.42 g,63.9 mmol) en 200 mL de THF seco a 0°C se agregó 4- ciano- 1,3- bencenodicarboxilato de dimetilo (Intermedio 39) (7.0 g, 31.9 mmol) en varios lotes. Luego la suspensión se calentó a temperatura ambiente y se agitó durante 6 horas. Después de enfriarse a 0 °C, se agregó 15 mL de MeOH cuidadosamente para apagar la reacción, seguido por 15 mL de agua. La mezcla resultante se agitó durante la noche. Luego la suspensión se filtró a través de 100 g de Celite y se lavó con MeOH (5 x 60 ml) . El filtrado combinado se concentró y se filtró al vacío para proporcionar [4- (aminometil) benzeno- 1,3- diil]dimetanol como un aceite marrón (5.0 g, 94%) .

LCMS (D) Rt = 0.26 minutos; m/z $[M+H]^+$ =168

^1H NMR (CD_3OD) δ 7.29- 7.46 (m, 3H) , 4.68 (s, 2H) , 4.63 (s, 2H) , 3.33 (s, 2H) .

Intermedio 41

2- cloro- 5- (metiltio) benzoato de metilo

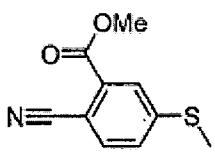


Una solución de ácido 2- cloro- 5- (metiltio) benzoico (20 g, 94.7 mmol) en MeOH (150 mL) se enfrío a 0 °C. Se agregó cloruro de tionilo (10 mL, 140 mmol) por goteo durante 10 minutos y la reacción se agitó a temperatura ambiente y la reacción se agitó a temperatura ambiente durante la noche. Luego el solvente se retiró. El sólido amarillo se retiró en 250 mL de acetato de etilo y se lavó con 30 mL) de bicarbonato de sodio saturado. La fase orgánica se separó, se secó sobre NaSO4 y se concentró para proporcionar 2- cloro- 5- (metiltio) benzoato de metilo como un sólido blanco 823.2 g, 100%) .

LCMS (D) Rt = 2.76 minutos; m/z $[M+H]^+$ =217

Intermedio 42

2- ciano- 5- (metiltio) benzoato de metilo

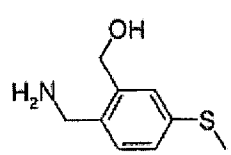


Se disolvió 2- cloro- 5- (metiltio) benzoato de metilo (Intermedio 41) (23.2 g, 106.9 mmol) y cianuro de cobre (I) (19.2 g, 213.8 mmol) en 100 mL de N- metilpirrolidinona. La mezcla resultante se calentó a 160 °C durante 72 horas. LCMS mostró la presencia de éster cianurazo y ácido hidrolizado en proporción 1:1. Luego de enfriar a temperatura ambiente, la mezcla de reacción se trató con 250 mL de agua y 300 mL de acetato de etilo y se filtró a través de Celite. Las fases se separaron. La fase acuosa se extrajo con 2 x 250 mL de acetato de etilo. Los orgánicos combinados se lavaron con 250 mL de agua, se secaron sobre $MgSO_4$ y se concentraron para dejar un aceite. El material crudo se purificó mediante columna de gel de sílice combi flash eluyendo con 0- 20% acetato de etilo en hexanos para proporcionar 2- ciano- 5- (metiltio) benzoato de metilo (6.14 g, 28%) como un sólido blanco.

LCMS (D) Rt = 2.42 minutos; m/z $[M+H]^+$ =208

Intermedio 43

[2- (Aminometil) - 5- (metiltio) fenil]metanol



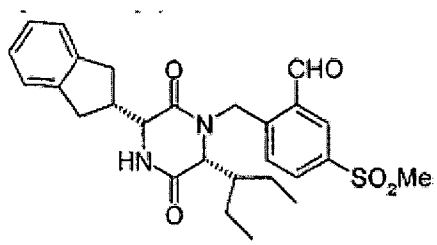
A una suspensión de hidruro de aluminio de litio (3.37 g, 88.9 mmol) en 70 mL de THF seco a 0 °C se agregó 2- ciano- 5- (metiltio) benzoato de metilo (intermedio 42 (6.14 g, 29.6 mmol) en varios lotes. Luego la suspensión se calentó a temperatura ambiente y se agitó durante 18 horas. Luego de enfriar a 0 °C, se agregó 15 mL de MeOH cuidadosamente para apagar la reacción , seguido por 15 mL de agua. La mezcla resultante se agitó a temperatura ambiente durante 3 horas. Luego la mezcla de suspensión se filtró a través de 50 g de Celite y se lavó con MeOH (5 x 60 mL) . El fltrado combinado se concentró y se secó al vacío para proporcionar [2- (aminometil) - 5- (metiltio) fenil]metanol (3.80 g, 70%) .

LCMS (D) Rt = 0.40 minutos; m/z $[M- NH_3]^+$ =167

^1H NMR (CD_3OD) δ 7.27 (d, 1H) , 7.26 (s, 1H) , 4.50 (s, 2H) , 3.70 (s, 2H) , 33.4 (bs, 1H) , 3.17 (s, 3H) , 1.92 (bs, 2H) .

Intermedio 44

2- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- 5- (metilsulfonil) benzaldehido

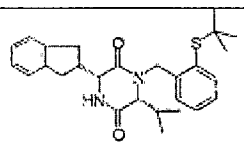


Se disolvió (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona (Ejemplo 206) (880 mg, 176 mmol) en diclorometano seco (5 ml) . Se agregó periodinano Dess- Martin (1.13 g, 2.64 mmol) . La suspensión resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción cruda se purificó directamente mediante columna de gel de sílice combi flash eluyendo con acetato de etilo al 0- 75% en hexanos para proporcionar 2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- 5- (metilsulfonil) benzaldehido (710 mg, 81%) como un sólido blanco.

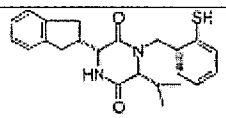
LCMS (D) Rt = 2.73 minutos; m/z $[M+H]^+$= 497

^{1}H NMR (CD_3OD) δ 10.26 (s, 1H) , 8.19 (s, 1H) , 7.92 (d, 1H) , 7.43 (d, 1H) , 7.22 (m, 2H) , 7.14 (m, 2H) , 5.75 (d, 1H) , 5.15 (dd, 1H) , 4.75 (dd, 1H) , 4.10 (m, 1H) , 4.01 (m, 1H) , 3.13 (s, 3H) , 3.09- 3.13 (m, 2H) , 2.92 (m, 2H) , 1.60- 1.75 (m, 4H) , 1.35 (m, 1H) , 0.96 (t, 3H) , 0.93.

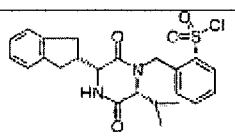
Intermedio 45 se preparó mediante un método análago al Ejemplo 1, utilizando ({2—[(1,1-dimetiletil) tio]fenil}metil) amina y 2- metilpropionaldehido

Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
45		450	3.8 (A)	451; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ([(1,1- dimetiletil) - tio]fenil}metil) - 6- (1- metil- etil) - 2,5- piperazinadiona

Intermedio 46 se preparó a partir del Intermedio 45 mediante un método análogo al Intermedio 19

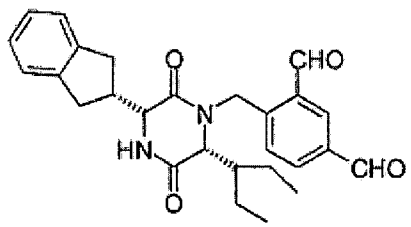
Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
46		394	3.4 (A)	495; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- mercaptofenil) - metil]- 6- (1- metiletil) - 2,5- piperazinadiona

Intermedio 47 se preparó a partir del Intermedio 46 mediante un método análogo al Intermedio 20.

Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
47		460	3.5	461; -	Cloruro de 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 2,5- dioxo- 1- piperazinil]metil}bencenosulfonilo

Intermedio 48

4- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 1- ,3- bencenodicarbaldehido



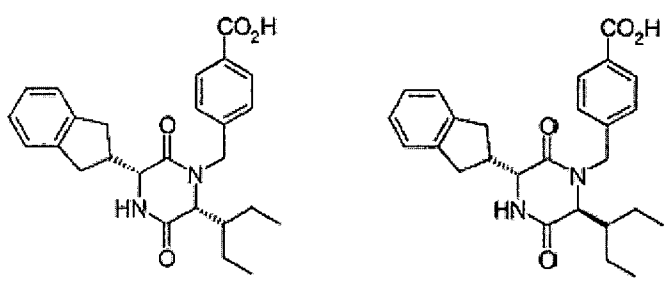
Se disolvió (3R,6R) - 1- {[2,4- Bis(hidroximetil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (Ejemplo 196) (490 mg, 1.1 mmol) en doclorometano seco (5 ml) . Se agregó periodinano Dess- Martin (1.38 g, 3.3 mmol) . La suspensión resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción cruda se purificó inmediatamente mediante columna de gel de sílice combi flash eluyendo con 0- 75% acetato de etilo en hexanos para proporcionar 4- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 1- ,3- bencenodicarbaldehido (485 mg, 100%) como un sólido blanco.

LCMS (D) Rt = 2.82 minutos; m/z $[M+H]^+$= 447

^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H) , 10.12 (s, 1H) , 8.39 (s, 1H) , 8.10 (d, 2H) , 7.51 (d, 1H) , 7.21- 7.28 (m, 3H) , 5.43 (d, 1H) , 4.98 (d, 1H) , 4.11- 4.19 (m, 1H) , 4.05 (s, 1H) , 3.18 (m, 3H) , 2.96- 3.02 (m, 1H) , 2.82- 2.88 (m, 1H) , 1.50- 1.70 (m, 4H) , 1.36- 1.41 (m, 1H) , 0.93 (t, 3H) , 0.88 (t, 3H) .

Intermedio 49

Mezcla diastereomérica del ácido 4- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benzóico y el ácido 4- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benzóico



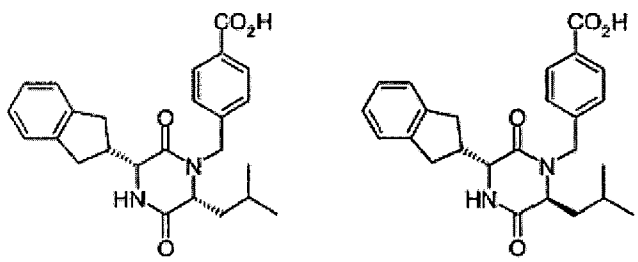
A una solución de 4- (aminometil) benzoato de 1,1- dimetiletil (0.79 g, 3.81 mmol) en trifluoroetanol (4 mL) se agregó 2- etilbutanal (0.47 mL, 3.81 mmol) y se agitó a temperatura

ambiente durante 30 minutos. Se agregó ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1-dimetiletil) - oxi]carbonil}amino) etanóico (1.11 g, 3.81 mmol) . La mezcla de reacción se calentó lentamente para disolver la glicina de indanilo. Después de agitar a temperatura ambiente durante 30 minutos, se agregó 4- clorofenilisonitrilo (0.52 g, 3.81 mmol) La reacción se agitó durante la noche (22 horas) y luego se enfrió en un baño de hielo/agua. Se agregó cloruro de acetilo (1.6 mL, 22.86 mmol) por goteo durante 30 minutos. El baño de hielo se retiro y la reacción se agitó a temperatura ambiente durante el fin de semana. La reacción se concentró bajo presión reducida para proporcionar un sólido marrón. Se agregó cloruro de metileno (20 mL) y una solución de bicarbonato de sodio acuoso saturado (20 mL) al residuo crudo y luego se agitó durante 30 minutos. Las fases se separaron y la fase acuosa se extrajo con EtOAc (3x) . La fase orgánica combinada se lavó con salmuera, se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar 1.0 g de un sólido marrón pegajoso. Se agregó cloroformo (20 mL) al residuo y la solución resultante se trató con ácido acético glacial (0.6 mL) y se agitó a temperatura ambiente durante la noche (16 horas) . La reacción se concentró para proporcionar un sólido marrón. Se agregó acetato de etilo al residuo y se extrajo con una solución $NaHCO_3$ acuosa saturada (3x) . Los extractos acuosos saturados se acidificaron con 2N HCl (pH = 2- 3) y se extrajeron de vuelta con acetato de etilo (3x) . Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) , filtraron y concentraron para proporcionar 0.42 g de los compuestos del título como un sólido amarillo.

HPLC (D) Rt = 2.70 minutos; m/z $[M+H]^+$= 435

Intermedio 50

Mezcla diastereomerica de ácido 4- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (2-metil- propil) - 2,5- dioxo- 1- piperazinil]- metil}benzóico y ácido 4- {[(3R,6R) - 3- (2,3-Dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benzóico

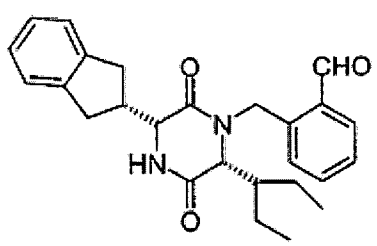


A una solución de 4- (aminometil) benzoato de 1,1- dimetiletil (0.70 g, 3.38 mmol) en metanol (4 mL) se agregó ácido (2R(- 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]- carbonil}amino) etanóico (0.98 g, 3.38 mmol) , seguido por 4- clorofenilisonitrilo (0.46 g, 3.38 mmol) y luego isovaleraldehido (0.37 mL, 3.38 mmol) . La reacción se agitó a temperatura ambiente durante la noche (18 horas) y se concentró bajo presión reducida para proporcionar un sólido amarillo. Se agregó cloruro de metileno (3 mL) al residuo y luego se enfrió a 0° C con un baño de hielo. Se agregó 4M dioxano de HCI (5 mL, 20.3 mmol) por goteo durante 30 minutos. El baño de hielo se removio y la mezcla de reacción se agitó a temperatura ambiente durante el fin de semana. La reacción se concentró bajo presión reducida para proporcionar un aceite marrón oscuro. Se agregó cloruro de metileno (20 mL) en una solución de bicarbonato de sodio acuosa saturada (10 mL) al residuo crudo y luego se agitó durante 30 minutos. Las fases se separaron . La fase orgánica se extrajo adicionalmente con una solución de $NaHCO_3$ acuosa saturada (3x) . Los extractos acuosos combinados se acidificaron con HCI 2N (pH = 2 – 3) y se extrajeron de vuelta con acetato de etilo (3x) . Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) , se filtraron y concentraron para proporcionar 1.01 g de los compuestos del título como un sólido amarillo.

HPLC (D) Rt = 2.61 minutos; m/z $[M+H]^+$= 421.

Intermedio 51

2- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxopiperazin- 1- il]- metil}benzaldehido



Se disolvió (3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [2- (hidroximetil) - benzil]piperazina- 2,5- diona (Ejemplo 1) (4.0.4 g, 9.6 mmol) en diclorometano seco (25 ml) conteniendo tamices moleculares 4A (3.43 g) . Se agregó N- oxido de 4- Metilmorfolina (1.6 g, 13.6 mmol) a la mezcla agitada seguido por perrutenato de tetrapropilamonio (101 mg, 0.29 mmol) . La mezcla se agitó a temperatura ambiente durante 90 minutos antes de cargar sobre una

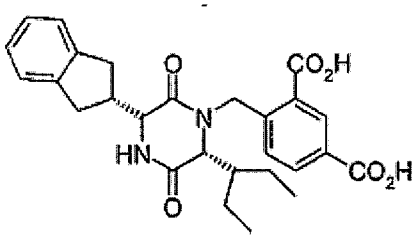
columna de cromatografía de gel de sílice rápida de 40 g (pre- eluida con ciclohexano) . La columna se eluyó con 0% a 100% acetato de etilo en ciclohexano para proporcionar 2- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxopiperazin- 1- il]- metil}benzaldehido (2.5 g) como un sólido color crema pálido.

HPLC (A) Rt = 3.35 minutos; m/z $[M+H]^+$= 419

^{1}H NMR ($CDCl_3$) δ 10.15 (s, 1H) , 7.86 (dd, 1H) , 7.59 (dt, 1H) , 7.52 (br t, 1H) , 7.32 (d, 1H) , 7.22 (m, 5H) , 5.47 (d, 1H) , 4.90 (d, 1H) , 4.15 (dd, 1H) , 4.00 (d, 1H) , 3.16 (m, 3H) , 2.97 (m, 1H) , 2.83 (dd, 1H) , 1.63 (m, 4H) , 1.34 (m, 1H) , 0.88 (m, 6H) .

Intermedio 52

Ácido 4- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}bencenodicarboxílico



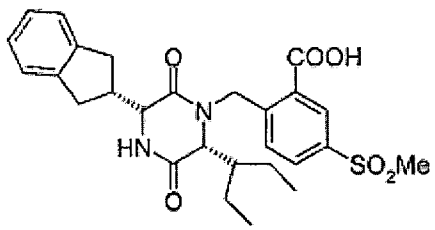
Se agregó una solución de ácido sulfámico (130 mg,1.30 mmol) en agua (2 mL) por goteo durante 5 minutos a una solución agitada de 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- 1,3- bencenodicarbaldehido (Intermedio 48) (490 mg, 1.10 mmol) en acetonitrilo (20 mL) , seguido por la adición por goteo de una solución de clorito de sodio (298 mg, 3.30 mmol) . Luego de agitar la mezcla a temperatura ambiente durante 90 minutos se evaporó bajo presión reducida para remover el solvente orgánico. El residuo acuoso se diluyó con 5 mL de agua y se extrajo con acetato de etilo (3 x 10 mL) . Los orgánicos combinados se lavaron con solución de cloruro de sodio acuoso saturado (10 mL) , se secó sobre $MgSO_4$, se evaporó bajo presión reducida y se secó al vacío para proporcionar ácido 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}bencenodicarboxílico como un sólido blanco (490 mg, 98%) .

LCMS (D) Rt = 2.47 minutos; m/z $[M+H]^+$= 479

^{1}H NMR (DMSO) δ 8.54 (s, 1H) , 8.43 (s, 1H) , 8.09 (d, 1H) , 7.35 (d, 1H) , 7.22 (s, 2H) , 7.12 (s, 2H) , 5.10 (d, 1H) , 4.87 (d, 1H) , 4.00- 4.05 (m, 1H) , 3.90 (s, 1H) , 3.10- 3.50 (bs, 1H) , 2.80- 3.10 (m, 5H) , 1.30- 1.60 (m, 4H) , 1.10- 1.25 (m, 1H) , 0.80 (t, 3H) , 0.70 (t, 3H) .

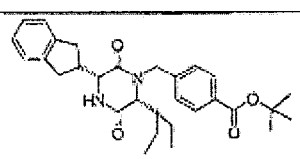
Intermedio 53

Ácido 2- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- (metilsulfonil) benzoico



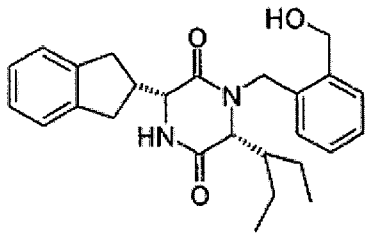
Se agregó una solución de ácido sulfámico (130 mg, 1.30 mmol) en agua (2 mL) a una solución agitada de 2- {[(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- 5- (metilsulfonil) benzaldehido (Intermedio 44) (500 mg, 1.00 mmol) en acetonitrilo (15 mL) , seguido por la adición por goteo de una solución de clorito de sodio (136 mg, 1.50 mmol) en agua (2 mL) . Luego de agitar la mezcla a temperatura ambiente durante 90 minutos se evaporó bajo presión reducida para remover el solvente orgánico. El residuo acuoso se diluyó con 10 mL de agua y se extrajo con acetato de etilo (3 x 10 mL) . Los orgánicos combinados se secaron sobre $MgSO_4$, se evaporaron bajo presión reducida y se secaron al vacío para proporcionar ácido 2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- (metilsulfonil) benzoico como un sólido blanco (520 mg, 99%) . LCMS (D) Rt = 2.54 minutos; m/z $[M+H]^+$= 513

El siguiente intermedio se preparó mediante un método análogo al Intermedio 15.

Int. No.	Estructura	Peso Mol.	Rt/ min	+ve ; - ve	Nombre
54		490.6	3.79 (A)	491	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 2,5- dioxo- 1- piperazinil]- metil}benzoato de 1,1- dimetiletilo

Ejemplo 1

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [2(hidroximetil) - bencil]piperazina- 2,5- diona

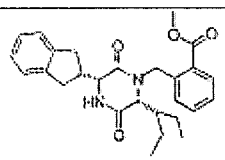
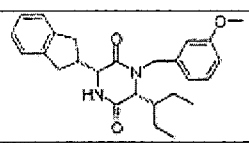
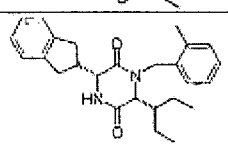
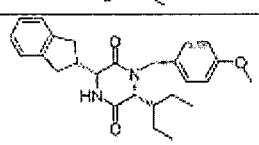
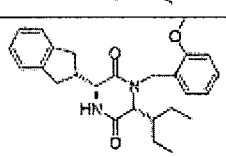
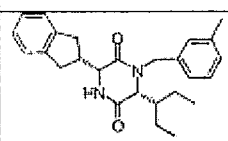


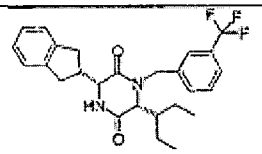
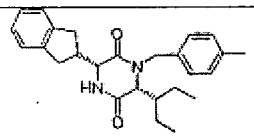
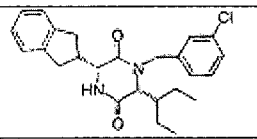
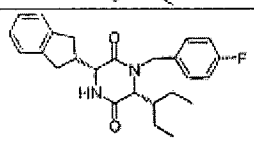
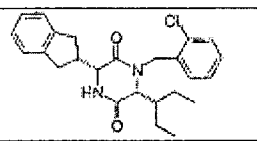
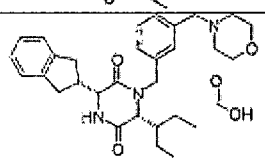
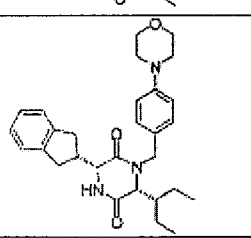
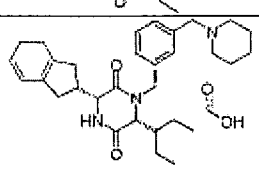
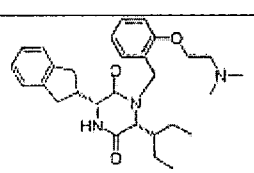
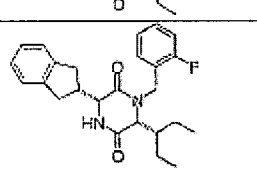
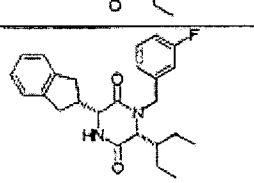
Se disolvió [2- aminometil) fenil]metanol (4.12g, 30 mmol) en metanol (30 ml) y se agregó 2-etilbutanal (3.7 mmol) seguido por ácido de (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1-dimetiletil) oxi]carbonil}amino) etanóico (8.74g, 30 mmol) . La mezcla se agitó durante 15 minutos antes de agregar 4- clorofenilisonitrilo (4.13g, 30 mmol) . La mezcla se agitó durante 2.25 horas y luego se dejo sentar a temperatura ambiente durante la noche (16.3 horas) antes de enfriarse en un baño de hielo/agua. Luego se agregó por goteo cloruro de acetilo (12.75ml, 179.5 mmol) , manteniendo la temperatura de reacción bajo 20°C. La mezcla de reacción se agitó en el baño de enfriamiento durante 10 minutos adicionales antes de ser agitada a temperatura ambiente. Después de 5 horas la mezcla fue evaporada bajo presión reducida para dejar una goma de color marrón oscuro. La goma se agitó en cloroformo (75ml) y una solución de bicarbonato de sodio acuoso saturado (75 ml) durante 20 minutos antes de diluirse con cloroformo (75 ml) y la fase fue separada. La fase acuosa fue extraída con cloroformo (3 x 75 ml) . La fase orgánica combinada fue secada sobre ($MgSO_4$) y concentrada bajo presión reducida a 75ml ca. La solución de cloroformo se trato con ácido acético glacial (3ml) y se dejo sentar a temperatura ambiente durante el fin de semana. Luego la mezcla de reacción fue lavada con ácido clorhídrico 2M (75 ml) , seguido por una solución de bicarbonato de sodio acuoso saturado (75 ml) . La fase orgánica fue secada ($MgSO_4$) y evaporada bajo presión reducida y secada para dejar una espuma marrón. La espuma se cargó en diclorometano sobre una columna de cromatografía de sílice rápida de 330g (pre- eluida con acetato de etilo al 20% en ciclohexano) . La columna fue diluida con 20% a 100% de acetato de etilo para proporcionar (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [2- hidroximetil) bencil]pipèrazina- 2,5- diona (4.12g) como un sólido marrón pálido.

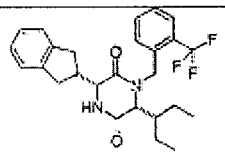
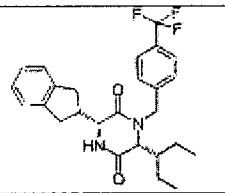
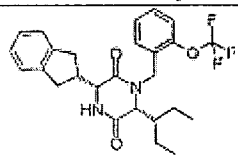
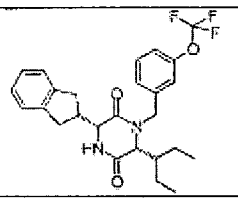
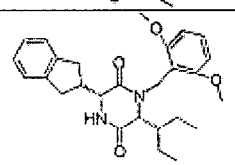
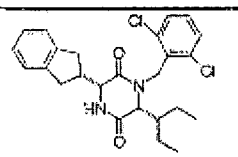
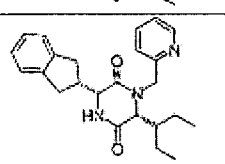
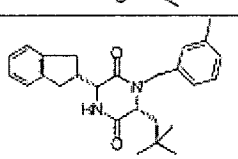
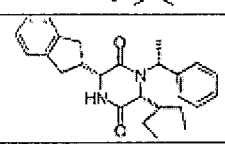
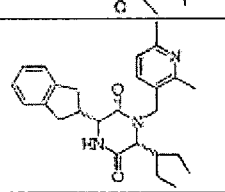
HPLC (A) Rt=3.26 minutos; m/Z $[M+H]^+$= 42.1

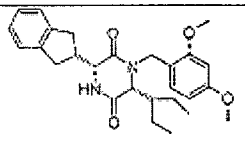
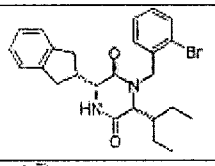
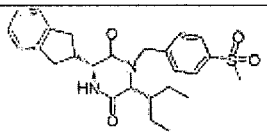
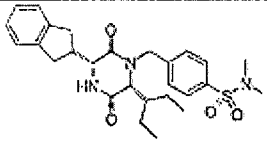
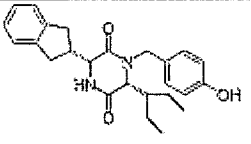
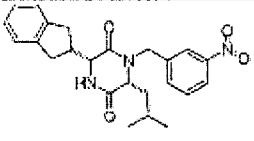
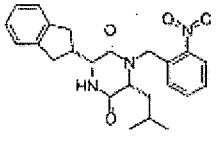
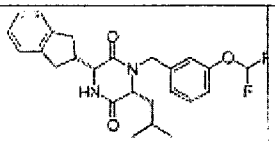
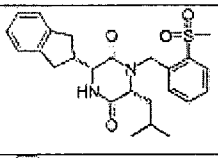
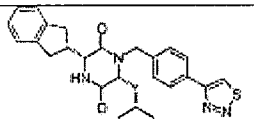
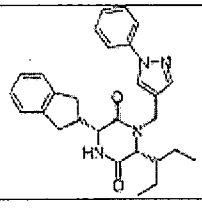
^{1}H NMR ($CDCl_3$) δ 7.37 (m, 1H) , 7.30 (m, 2H) , 7.21 (m, 5H) , 6.84 (br d, 1H) , 5.45 (d, 1H) , 4.74 y 4.63 (d, 1H) , 4.08 (dd, 1H) , 4.04 (d, 1H) , 3.15 (m, 3H) , 2.92 (m, 1H) , 2.78 (m, 2H) , 1.76 (m, 1H) , 1.62 (m, 3H) , 1.31 (m, 1H) , 0.92 (m, 6H) .

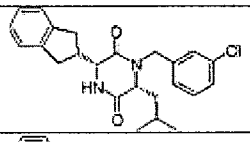
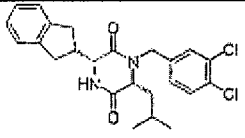
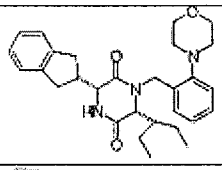
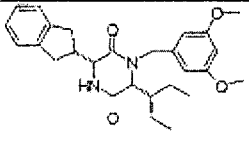
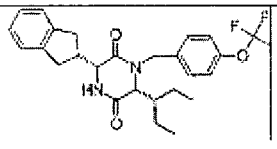
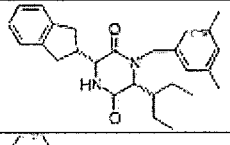
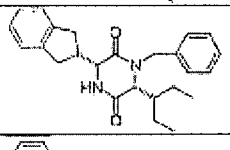
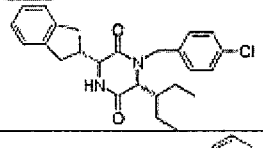
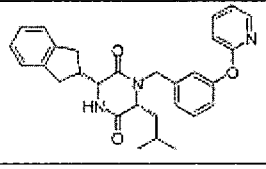
Los ejemplos 2- 12, 17- 31, 33, 43- 47 se prepararon mediante métodos análogos a aquel descrito en el ejemplo 1 utilizando 4- clorofenilisonitrilo, opcionalmente con la adición de una base tal como trietilamina o DIPEA si las sales hidrocloruro de aminas fueron utilizadas. En una modificación de este método, los **ejemplos 13- 16, 32, 34- 42, 48** se prepararon en una manera análoga al ejemplo 124, utilizando isocianuro de 2- {[(1,1- dimetiletil) (dimetil) sili]oxi}- fenilo, opcionalmente con la adición de una base tal como trietilamina o DIPEA si las sales de hidrocloruro de aminas fueron utilizadas.

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve ; - ve	Nombre
2		448.5	3.47 (A)	449; 447	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 2,5- dioxo- 1- piperazinil]- metil}- benzoato de metilo
3		420.6	3.50 (A)	421; 419	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[3- metoxi- fenil]metil}- 2,5- piperazinadiona
4		404.6	3.59	405; 403	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- [(2- metilfenil) metil]- 2,5- piperazinadiona
5		420.6	3.48 (A)	421; 419	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[4- metoxi- fenil]metil}- 2,5- piperazinadiona
6		420.6	3.54 (A)	421; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[2- (metoxi) fenil]metil}- 2,5- piperazinadiona
7		404.6	3.60 (A)	405; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona

8		458.5	3.63 (A)	459; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[3- (trifluorometil) fenil]metil}- 2,5- piperazinadiona
9		404.6	3.62 (A)	405; 403	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- [(4- metilfenil) metil]- 2,5- piperazinadiona
10		425.0	3.65 (A)	425; 423	(3R, 6R) - 1- [(3- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 2,5- piperazinadiona
11		408.5	3.51 (A)	409; 407	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- [(4- fluorofenil) metil]- 2,5- piperazinadiona
12		425.0	3.66	425; 423	(3R, 6R) - 1- [(2- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 2,5- piperazinadiona
13		535.7	2.58 (A)	490; 488	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[3- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona formato
14		475.6	3.38 (A)	476; 474	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[4- (4- morfolin) fenil]metil}- 2,5- piperazinadiona
15		533.7	2.65 (A)	488; 486	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[3- (1- piperidinilmetil) - fenil]metil}- 2,5- piperazinadiona formato
16		477.7	2.67 (A)	478; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[2- (dimetilamino) - metil]- 6- (1- etilpropil) - 2,5- piperazinadiona
17		408.5	3.54 (A)	409; 407	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- fluorofenil) metil]- 2,5- piperazinadiona
18		408.5	3.54 (A)	409; 407	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(3- fluorofenil) metil]- 2,5- piperazinadiona

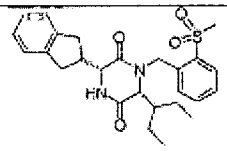
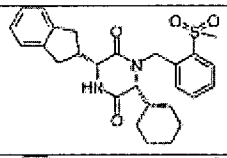
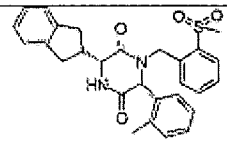
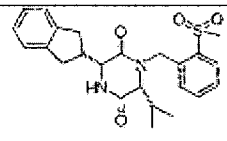
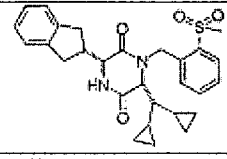
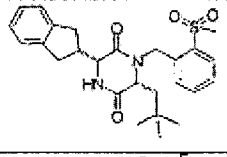
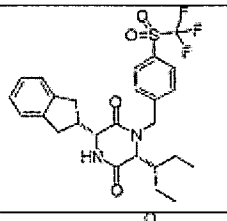
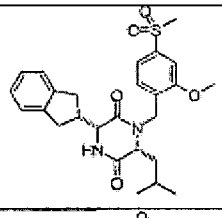
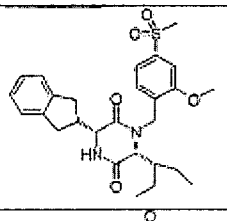
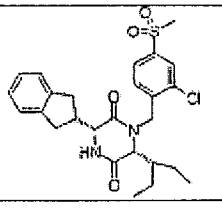
19		458.5	3.73 (A)	459; 457	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (trifluorometil) fenil]metil}- 2,5- piperazinadiona
20		458.5	3.70 (A)	459; 457	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilproil) - 1- {[4- (trifluorometil) fenil]metil}- 2,5- piperazinadiona
21		474.5	3.73 (A)	475; 473	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- [(trifluorometil) foxi]fenil}metil) - 2,5- piperazinadiona
22		474.5	3.73 (A)	475; 473	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({3- [(trifluorometil) foxi]fenil}metil) - 2,5- piperazinadiona
23		450.6	350 (A)	451 -	(3R, 6R) - 1- {[2,6- bis(metoxi) - fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
24		459.4	3.74 (A)	459; 461; 455/ 457	(3R, 6R) - 1- [(2,6- diclorofenil) - metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
25		391.5	3.09 (A)	392; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- piridinilmetil) - 2,5- piperazinadiona
26		404.6	3.69 (A)	405; 403	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2,2- dimetilpropil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona
27		404.6	3.58 (A)	405; 403	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1R) - 1- feniletil]- 2,5- piperazinadiona
28		419.6	2.51 (A)	421; 418	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2,6- dimetil- 3- piridinil) - metil]- 6- (1- etilpropil) - 2,5- piperazinadiona

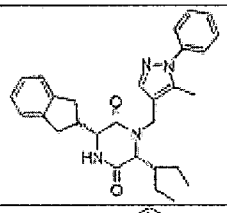
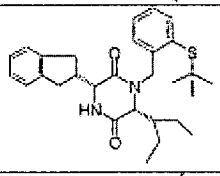
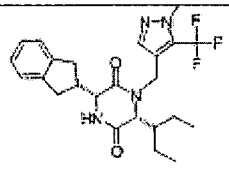
29		450.6	3.53 (A)	451; -	(3R, 6R) - 1- {[2,4- bis(metoxi) - fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
30		469.4	3.78 (A)	469/ 471; 467/ 469	(3R, 6R) - 1- [(2- bromofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
31		468.6	3.0 (A)	469; 467	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona
32		497.7	3.3 (A)	498; 496	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetil- bencenosulfonamida
33		406.5	3.29 (A)	407; 405	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- hidroxifenil) metil]- 2,5- piperazinadiona
34		421.5	3.34 (A)	422; 420	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(3- nitrofenil) metil]- 2,5- piperazinadiona
35		421.5	3.35 (A)	422; 420	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- nitrofenil) metil]- 2,5- piperazinadiona
36		442.5	3.42 (A)	443; 441	(3R, 6R) - 1- ({3- [(difluorometil) oxi]fenil}metil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona
37		454.6	3.25 (A)	455; 453	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona
38		460.6	3.49 (A)	461; 459	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (1,2,3- tiadiazol- 4- il) fenil]metil}- 2,5- piperazinadiona
39		456.6	3.55 (A)	457; 455	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- fenil- 1H- pirazol- 4- il)) metil]- 2,5- piperazinadiona

40		410.9	3.52 (A)	411; 409	(3R, 6R) - 1- [(3- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona
41		445.4	3.65 (A)	445; 443	(3R, 6R) - 1- [(3,4- diclorofenil) - metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona
42		475.6	3.47 (A)	476; 474	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolin) fenil]metil}- 2,5- piperazinadiona
43		450.6	3.48 (A)	451; 449	(3R, 6R) - 1- {[3,5- bis(metoxi) - fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
44		474.5	3.75 (A)	475; 473	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(trifluorometil) oxi]fenil}metil) - 2,5- piperazinadiona
45		418.6	3.74 (A)	419; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3,5- dimetilfenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona
46		390.5	3.51 (A)	391; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (fenil- metil) - 2,5- piperazinadiona
47		425.0	3.66 (A)	425; 423	(3R, 6R) - 1- [(4- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
48		469.9	3.37 (A)	470; 468	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[3- (2- piridiniloxi) fenil]metil}- 2,5- piperazinadiona

Los Ejemplos 49- 61 se prepararon mediante métodos análogos a aquel descrito para el Ejemplo 1, utilizando los intermedios indicados, opcionalmente con la adición de una base tal como trietilamina o DIPEA si se utilizaron sales de hidrocloruro de aminas.

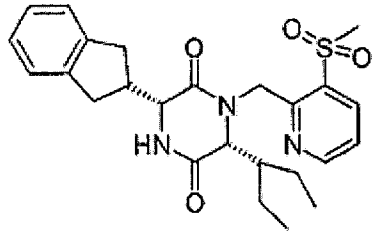
Ej. No.	Int. No.		Peso Mol.	Rt/ min	+ve; - ve	Nombre

49	1		468.6	3.3 (A)	469; 467	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona
50	1		480.6	3.37 (A)	481; 479	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona
51	1		488.6	3.19 (A)	489; 487	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilfenil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona
52	1		376.5	3.36 (A)	377; 375	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona
53	1		492.6	3.55 (A)	429; 427	(3R, 6R) - 6- (diciclopropilmetil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona
54	1		468.6	3.32 (A)	469; 467	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2,2- dimetil- propil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona
55	2		522.3	3.5 (A)	523; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [trifluorometil) - sulfonil]fenil}metil) - 2,5- piperazinadiona
56	3		484.6	3.3 (A)	485; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- metoxi- 4- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona
57	3		498.7	3.2 (A)	499;-	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- metoxi- 4- (metilsulfonil) - fenil]- metil}- 2,5- piperazinadiona
58	4		503.1	3.2 (A)	503; -	(3R, 6R) - 1- {[2- cloro- 4- (metil- sulfonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) fenil]- 2,5- piperazinadiona

59	5		470.6	3.31 (A)	471; 515	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(5- metil- 1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona
60	6		478.7	4.0 (A)	479; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- [(1,1- dimetil- etil) tio]fenil}- metil) - 6- (1- etilpropil) - 2,5- piperazinadiona
61	7		462.5	3.47 (A)	463; 461	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[1- metil- 5- (trifluorometil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona

Ejemplo 62

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (metilsulfonil- 2- piperidinil}- 2,5- piperazinadiona



Se disolvió 1- [3- (metilsulfonil) - 2- piridinil]metanamina (186 mg, 1 mmol) y 2- etilbutanal (124 uL, 1 mmol) en cloroformo (5 ml) y la mezcla de reacción se dejo a temperatura ambiente durante 63 horas. Se agregó ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]- carbonil}etanóico (291 mg, 1 mmol) , seguido por 4- clorofenilisonitrilo 8138 mg, mmol) y la mezcla se agitó durante 30 minutos a temperatura ambiente, luego se dejo durante 48 horas. El solvente se purgó con nitrógeno, el residuo se retiró en metanol (10 mL) y la solución fue enfriada a 0°C, luego se agregó cuidadosamente por goteo cloruro de acetilo (0.5 mL) . La mezcla se dejo a temperatura ambiente durante la noche, luego el solvente fue purgado con nitrógeno y el residuo se retiró en diclorometano (10 mL) y se agitó con carbonato de hidrogeno de sodio saturado (5 mL) , agregando carbonato de hidrógeno de sodio con cuidado hasta que la

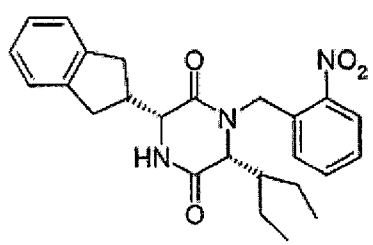
efervescencia terminó. La fase orgánica fue separada utilizando una frita hidrofóbica, y tratada con ácido acético glacial (0.1 mL) la mezcla se dejo a temperatura ambiente durante la noche. Luego se agitó con carbonato de hidrogeno de sodio acuoso saturado(5 mL) , agregando carbonato de hidrogeno de sodio sólido con cuidado hasta que la efervescencia terminó, luego la fase orgánica fue separada utilizando una frita hidrofóbica. El solvente fue removido bajo presión reducida y el producto crudo se purificó mediante cromatografía autoprep *(mass directed)* seguida por cromatografía de capa preparativa sobre sílice (placas de 20x20 cm, 2 mm de grosor) eluida x 3 con 2.5% isopropanol en diclorometano para proporcionar (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (metilsulfonil- 2- piperidinil}- 2,5- piperazinadiona (33 mg) como un sólido blancuzco.

HPLC (A) Rt= 3.18 mins, $[M+H]^+$ =470

^{1}H NMR ($CDCl_3$) δ 8.72 (dd, 1H) , 8.30 (dd, 1H) , 7.72 (br d, 1H) , 7.42 (dd, 1H) , 7.23- 7.14 (m, 4H) , 5.41 (d, 1H) , 5.03 (d, 1H) , 4.47 (d, 1H) , 4.00 (dd, 1H) , 3.42 (s, 3H) , 3.18- 2.80 (m, 5H) , 1.85- 1.61 (m, 4H) , 1.48- 1.35 (m, 1H) , 1.04- 0.95 (m, 6H) .

Ejemplo 63

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- nitrobencil) piperazina- 2,5- diona



Se disolvió hidrocloruro de [(2- nitrofenil) metil]amina en acetato de etilo (25 ml) y se agregó carbonato de hidrógeno de sodio (25 ml) . La fase orgánica fue separada, secada (Na_2SO_4) y concentrada para proporcionar [(2- nitrofenil) metil]amina como un aceite amarillo (2.48g, 61.4%) .

HPLC Rt = 0.46 minutos; m/z $[M+H]^+$ = 153.

A una solución de [(2- nitrofenil) metil]amina (2.48 g, 16.2 mmol) en metanol (50 ml) se agregó ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}- amino) - etanóico

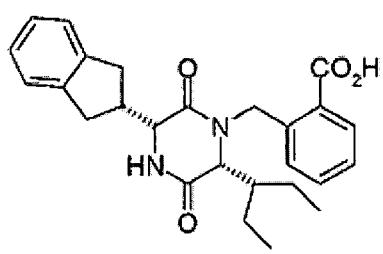
(4.72 g, 16.2 mmol) , isocianuro de 2- {[(1,1- dimetiletil) (dimetil) silil]oxi}fenil (3.78 g, 16.2 mmol) y 2- etilbutanal (2 ml, 16.2 mmol) . La reacción se agitó a temperatura ambiente durante 18 horas luego enfriada a 0°C y se agregó cloruro de acetilo (6.9 ml) . La reacción se agitó a temperatura ambiente durante 72 horas. El solvente fue removido al vacío y el residuo disuelto en cloroformo (125 mL) . Se agregó bicarbonato de sodio (125 ml) y la mezcla bifásica agitada durante 3 horas. La fase orgánica fue separada, secada (Na_2SO_4) y concentrada. El residuo fue disuelto en cloroformo (120 ml) y se agregó ácido acético (1.2 ml) y la reacción se agitó a temperatura ambiente durante 18 horas y luego a 50 °C durante 1.5 horas. Luego la reacción se lavó con ácido clorhídrico (2M, 3 x 100 ml) . La fase orgánica fue separada, secada (Na_2SO_4) y concentrada para proporcionar un sólido marrón el cual se purificó mediante cromatografía de columna de sílice para proporcionar (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- nitrobencil) piperazina- 2,5- diona como un sólido marrón claro (2.88g, 44.4%).

HPLC (A) Rt= 3.39 minutos, m/z $[M+H]^+$ =436

^1H NMR ($CDCl_3$) δ 8.07 (dd, 1H) , 7.62 (dt, 1H) , 7.48 (dt, 1H) , 7.33 (d, 1H) , 7.24 (m, 2H) , 7.19 (m, 2H) , 6.47 (d, 1H) , 5.3 (d, 1H) , 4.72 (d, 1H) , 4.14 (m, 1H) , 4.02 (d, 1H) , 3.17 (m, 3H), 2.97 (m, 1H) , 2.8 (m, 1H) , 1.64 (m, 4H) , 1.35 (m, 1H) 0.93 (t, 3H) , 0.86 (t, 3H) .

Ejemplo 65

Ácido [(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico



Se agregó una solución de ácido sulfámico (750 mg, 7.72mmol) en agua por goteo durante 5 minutos a una solución agitada de 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxopiperazin- 1- il]metil}benzaldehido (int. 51) (2.48g, 5.92 mmol) en acetonitrilo (300ml) , seguido por la adición por goteo de una solución de clorato de sodio (775mg, 8.57 mmol) en agua (30ml) . Después de agitar la mezcla a temperatura ambiente

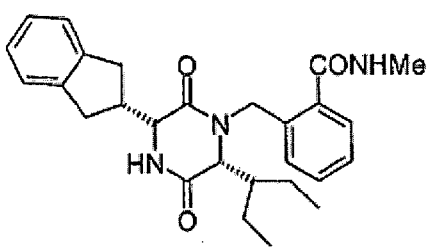
durante 70 minutos ésta se evaporó bajo presión reducida para remover el solvente orgánico. El residuo acuoso fue particionado entre acetato de etilo (150 ml) y agua (10 ml) . La fase orgánica fue lavada con una solución de cloruro de sodio acuoso saturado, secada ($MgSO_4$) , evaporada bajo presión reducida y secada al vacío para proporcionar el ácido [(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico como un sólido blanco (2.5g) .

HPLC (A) Rt= 3.39 minutos, m/z $[M+H]^+$ =435

^1H NMR ($CDCl_3$) δ 8.27 (dd, 1H) , 7.98 (d, 1H) , 7.53 (dt, 1H) , 7.38 (br t, 1H) , 7.35 (d, 1H) , 7.23 (m, 2H) , 7.16 (m, 2H) , 5.30 (d, 1H) , 4.68 (d, 1H) , 4.15 (d, 1H) , 4.12 (dd, 1H) , 3.16 (m, 3H) , 2.94 (m, 1H) , 2.87 (m, 1H) , 1.68 (m, 2H) , 1.58 (m, 2H) 1.34 (m, 1H) , 0.93 (t, 3H) , 0.87 (t, 3H) .

Ejemplo 66

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida



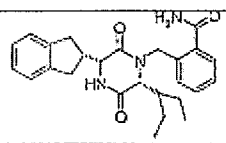
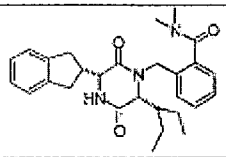
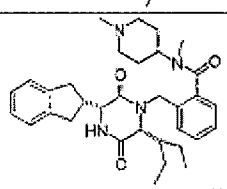
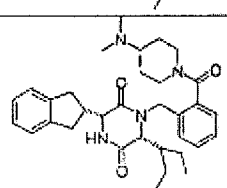
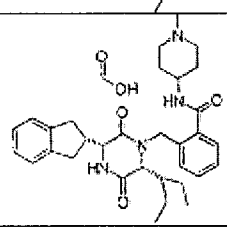
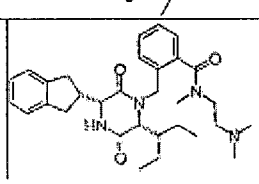
Se disolvió ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico (Ej. 65) (100mg, 0.23 mmol) en diclorometano seco (3 ml) y se agregó trietilamina (64ul, 0.46 mmol) , seguido después de 7 minutos por tetrafluoroborato de 2- (1H- benzotriazol- 1- il) - 1,1,33- tetrametiluronio (88 mg, 0.27 mmol) . La mezcla se agitó a temperatura ambiente durante 5 horas antes de agregar metilamina (0.6ml de una solución 2M en tetrahidrofurano, 1.2 mmol) . La mezcla se dejo sentar a temperatura ambiente durante la noche (17 horas) antes de ser diluida con diclorometano (2ml) y lavada con una solución de bicarbonato de sodio acuoso saturado. La fase orgánica fue secada (frita hidrofóbica) y evaporada para dejar una goma amarilla. La goma fue purificada utilizando cromatografía autoprep *(mass directed)* para proporcionar 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6-

(1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida como un sólido blanco (73mg) .

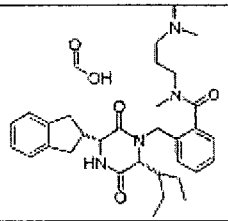
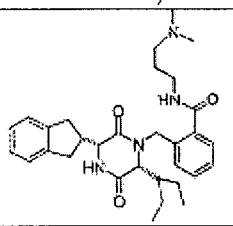
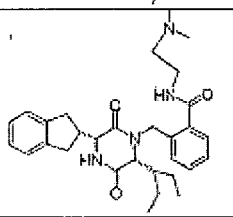
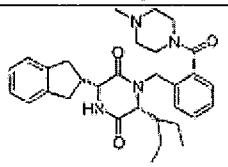
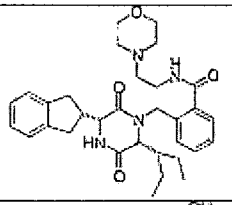
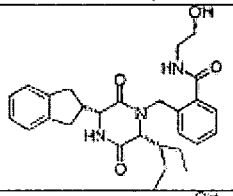
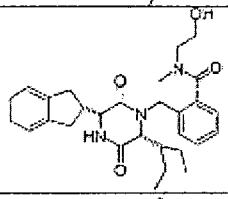
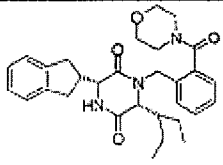
HPLC (A) Rt= 3.09 minutos, m/z $[M+H]^+$ =448

^1H NMR ($CDCl_3$) δ 7.54 (br s, 1H) , 7.40 (m, 2H) , 7.28 (m, 2H) , 7.20 (m, 4H) , 6.60 (br, q, 1H) , 5.13 (d, 1H) , 4.47 (d, 1H) , 4.11 (d, 1H) , 4.03 (dd, 1H) , 3.12 (m, 3H) , 3.00 (d, 3H) , 2.91 (m, 1H) , 2.80 (m, 1H) , 1.73 (m, 1H) , 1.61 (m, 3H) , 1.34 (m, 1H) 0.96 (t, 3H) , 0.89 (t, 3H) .

Los ejemplos 67- 80 se prepararon mediante métodos análogos a aquel descrito para el ejemplo 66 a partir de ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico (Ej. 65)

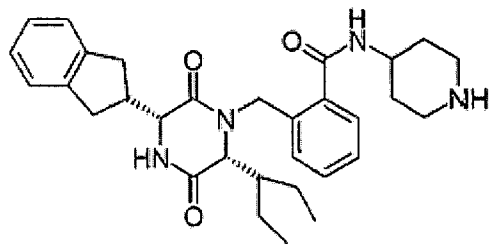
Ej.. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
67		433.5	3.05	434; 432	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida
68		461.6	3.2 (A)	462; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N,N- dimetilbenzamida
69		544.7	2.63 (A)	545; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metil- M- (1- metil- 4- piperidinil) benzamida
70		544.7	2.57 (A)	545;	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[4- (1- dimetilamino) - 1- piperidinil]carbonil}fenilmetil]- 6- (1- etilpropil) - 2,5- piperazinadiona
71		576.7	2.52 (A)	531; 529	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (1- metil- 4- piperidinil) benzamida formato
72		518.7	2.65 (A)	519; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (dimetil- amino) etil]- N- metilbenzamida

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73		578.7	2.65 (A)	533; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [3- (dimetil- amino) propil]- N- metilbenzamida
74		518.7	2.57 (A)	519; 517	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [3- (dimetil- amino) propil]benzamida
75		504.6	2.50 (A)	505; 503	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (dimetil- amino) etil]benzamida
76		516.6	2.54 (A)	517; 515	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(4- metil- 1- piperazinil) carbonil]fenil}- metil) - 2,5- piperazinadiona.
77		546.7	2.57 (A)	547; 545	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (4- morfolinil) etil]benzamida
78		477.6	2.91 (A)	478; 476	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) benzamida
79		491.6	3.06 (A)	492; 490	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxi- etil) - N- metilbenzamida
80		503.6	3.19 (A)	504; 502	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona.

Ejemplo 83

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- 4- piperidinilbenzamida



Se trató 4- {[(2- {[(3- R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) carbonil]amino}- 1- piperidinacarboxilato de 1,1- dimetiletilo (Int. 17) (845mg, 1.37 mmol) con cloruro de hidrogeno 4M en dioxano (3ml, 12 mmol) . La mezcla se agitó a temperatura ambiente durante 1 hora antes de evaporar bajo presión reducida para dejar una espuma amarilla. La espuma se cargó en 1:1 metanol: diclorometano sobre una columna SCX- SPE (pre- eluida con metanol) . La columna fue eluida con metanol, seguido por amoniaco 2M en metanol. El amoniaco en fracciones de metanol proporcionó 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- 4- piperidinilbenzamida como un sólido amarillo pálido (547mg) .

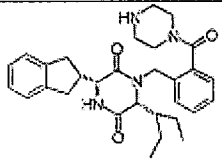
HPLC (A) Rt= 2.54 minutos, m/z $[M+H]^+$ =517

^1H NMR ($CDCl_3$) δ 7.44 (br d, 1H) , 7.38 (br t, 1H) , 7.31 (br t, 1H) , 7.24 (m, 2H) , 7.18 (m, 4H) , 6.78 (m, 1H) , 5.12 (d, 1H) , 4.45 (d, 1H) , 4.13 (d, 1H) , 4.07 (m, 1H) , 4.03 (dd, 1H) , 3.12 (m, 5H) , 2.91 (m, 1H) , 2.78 (m, 3H) , 2.06 (m, 2H) , 1.73 (m, 1H) 1.61 (m, 3H) , 1.45 (m, 2H) , 1.35 (m, 1H) , 0.96 (t, 3H) , 0.89 (t, 3H) .

Ejemplo 84 se preparó a partir del intermedio 18 mediante un método análogo a aquel descrito para el ejemplo 83

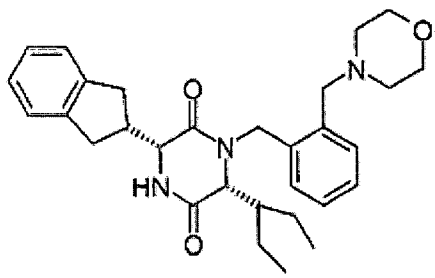
Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre

259

84		502.6	2.59 (A)	503; 501	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperazinilcarbonil) fenil]metil}- 2,5- piperazinadiona.

Ejemplo 85

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona



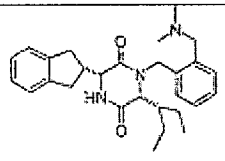
Se disolvió 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxopiperazin- 1- il]- metil}benzaldehido en tetrahidrofurano seco (2.5 ml) , bajo nitrógeno, y se agregó morfolina (34.5ul, 0.39 mmol) . La mezcla agitada se enfrió en un baño de hielo/agua y se agregó por goteo triacetoxiborohidruro de sodio (118mg, 0.55 mmol) . La mezcla se agitó durante 1.3 horas en el baño de enfriamiento antes de agitar a temperatura ambiente durante 3 días. Luego la mezcla se particionó entre una solución de cloruro de amonio acuoso saturado (2 ml) y diclorometano (5ml) . La fase orgánica fue lavada con una solución de bicarbonato de sodio acuoso saturado (2ml) , secada (frita hidrofóbica) y evaporada para dejar un sólido de color servato. El sólido se cargó en diclorometano sobre una columna SCX- SPE (cartucho 5g, pre- eluida con metanol) . La columna fue eluida con metanol, seguido por amoniaco 2M en metanol. El amoniaco en fracciones de metanol proporcionó (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona como un sólido anaranjado/marrón (145mg) .

HPLC (A) Rt= 2.70 minutos, m/z $[M+H]^+$ =490

^1H NMR ($CDCl_3$) δ 8.65 (br d, 1H) , 7.27 (m, 4H) , 7.19 (m, 4H) , 5.41 (d, 1H) , 4.47 (d, 1H) , 4.15 (dd, 1H) , 3.98 (d, 1H) , 3.70 (m, 4H) , 3.5 (ABq, 2H) , 3.21 (m, 2H) , 3.14 (m, 1H) , 2.97 (m, 1H) , 2.89 (m, 1H) , 2.44 (m, 4H) , 1.69 (m, 4H) , 1.35 (m, 1H) 0.98 (t, 3H) , 0.90 (t, 3H) .

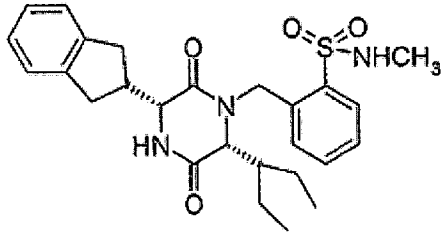
260

Ejemplo 86 se preparó mediante un método análogo a aquel descrito para el ejemplo 85.

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
86		447.6	2.59 (A)	448;	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(dimetilamino) metil]fenil}- metil) - 6- (1- etilpropil) - 2,5- piperazinadiona.

Ejemplo 89

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbencenosulfonamida



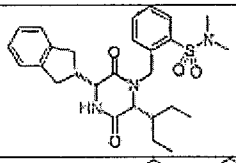
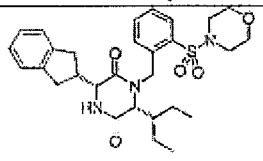
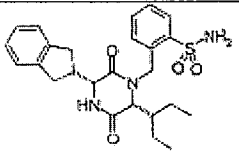
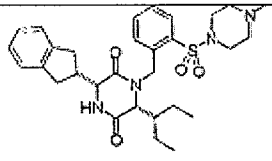
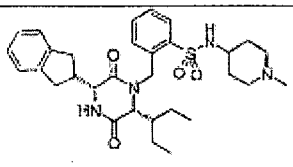
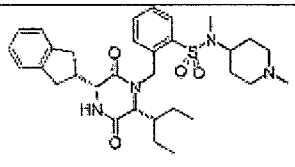
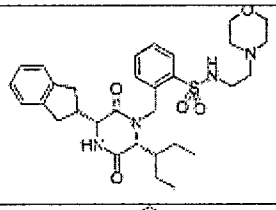
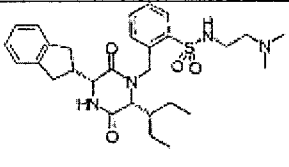
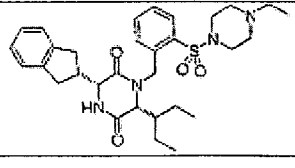
A una solución de cloruro 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbencenosulfonamida (Int. 20) (100mg) en diclorometano (2ml) se agregó diisopropiletilamina (39ul) y metilamina (2M, 0.31ml, 3 equivalente., NB generalmente 3 equivalente de aminas volátiles, 1 equivalente de aminas no-volátiles) y la mezcla se agitó durante 3 horas a 20°C. Se agregó metanol (2ml) y la mezcla se pasó a través de una columna de aminopropilo- SPE de 2g para proporcionar el producto (85mg, 83%) .

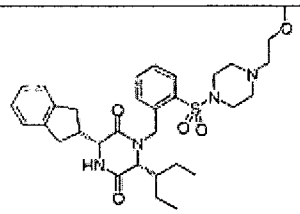
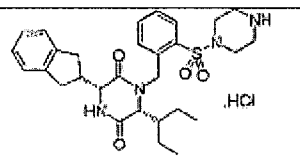
HPLC (A) Rt= 3.4 minutos, m/z $[M+H]^+$ =484

^{1}H NMR δ 8.03 (d, 1H) , 7.54 (t, 1H) , 7.45 (t, 1H) , 7.32 (d, 1H) , 7.22 (m, 4H) , 6.47 (br d, 1H) , 5.68 (q, 3H) , 5.58 (d, 1H) , 4.44 (d, 1H) , 4.1 (m, 2H) , 3.18 (m, 3H) , 2.96 (m, 1H) , 2.81 (dd, 1H) , 2.68 (d, 3H) , 1.4- 1.8 (m, 5H) , 0.96 (2t, 6H) .

Ejemplos 90- 100 se prepararon mediante métodos análogos a aquel descrito para el ejemplo 89

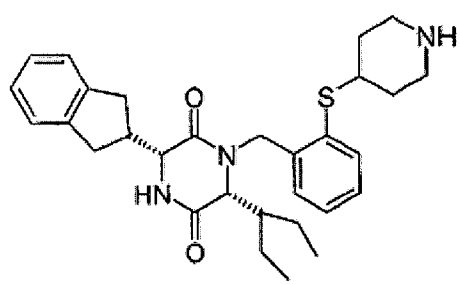
Ej.	Estructura	Peso	Rt/	+ve,	Nombre

No.		Mol.	min	- ve	
90		447.7	3.4 (A)	498; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]metil}- N,N- dimetil- bencenosulfonamida.
91		539.7	3.4 (A)	540; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilsulfonil) fenil]- metil}- 2,5- piperazinadiona.
92		469.6	3.2 (A)	470; 468	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]metil}- benceno- sulfonamida.
93		552.7	2.6	553; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 1- ({2- [(4- metil- 1- piperazinil) sulfonil]- fenil}- metil) - 2,5- piperazina.
94		566.8	2.6 (A)	567; 565	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]metil}- N- (1- metil- 4- piperidinil) - benceno- sulfonamida.
95		580.8	2.7 (A)	581; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]metil}- N- metil- N- (1- metil- 4- piperidinil) - benceno- sulfonamida.
96		582.8	2.7 (A)	538; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (4- morfolinil) etil]benceno- sulfonamida.
97		540.7	2.7 (A)	541; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (dimetilamino) etil]benceno- sulfonamida.
98		566.8	2.8 (A)	567; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(4- etil- 1- piperazinil) - sulfonil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona.

99		596.8	2.8 (A)	597; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- ({4- [2- (metoxi) etil]- 1- piperazinil}- sulfonil) fenil]metil}- 2,5- piperazinadiona.
100		575.2	2.7 (A)	539; -	Hidrocloruro de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperazinilsulfonil) fenil]metil}- 2,5- piperazinadiona.

Ejemplo 102

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- piperidiniltio) - fenil]metil}- 2,5- piperazinadiona



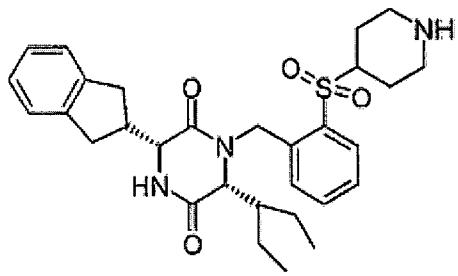
A una solución de 4- {[(2- {[(3- R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) tio]- 1- piperidinacarboxilato de 1,1- dimetiletilo (Int. 21) (45mg) en diclorometano (0.2mL) se agregó cloruro de hidrogeno 4M en dioxano (0.1 mL) y la mezcla se agitó durante dos horas. La mezcla fue reducida y purificada mediante aminopropilo- SPE y cromatografía autoprep *(mass directed)* para proporcionar el compuesto del titulo (12.2mg) .

HPLC (A) Rt= 2.8 minutos, m/z $[M+H]^+$ =506

^{1}H NMR δ 7.45 (m, 1H) , 7.20 (m, 7H) , 6.54 (br s, 1H) , 5.32 (d, 1H) , 4.51 (d, 1H) , 4.17 (dd, 1H) , 4.02 (d, 1H) , 3.20 (m, 5H) , 3.00 (m, 1H) , 2.84 (dd, 1H) , 2.75 (t, 2H) , 1.95- 2.20 (br m, 5H) , 1.70 (m, 5H) , 1.32 (m, 1H) ,0.92 (m, 6H) .

Ejemplo 104

Hidrocloruro de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- piperidinilsulfonil) - fenil]metil}- 2,5- piperazinadiona



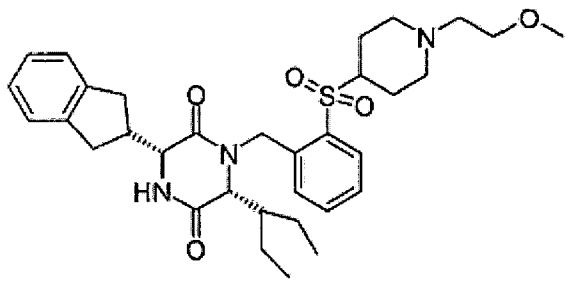
A una solución de 4- [(2- {[(3- R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) sulfonil]- 1- piperidinacarboxilato de 1,1- dimetiletilo (Int. 22) (94mg) en diclorometano (0.4mL) se agregó cloruro de hidrógeno 4M en dioxano (0.27 mL) y la mezcla se agitó durante 3 días. El solvente se removió al vacío para proporcionar el compuesto del titulo (80mg) .

HPLC (A) Rt= 2.7 minutos, m/z $[M+H]^+$ =538

^1H NMR ($CDCl_3$) δ 8.80 (br s, 2H) , 8.53 (br d, 1H) , 7.88 (d, 1H) , 7.78 (t, 1H) , 7.59 (t, 1H) , 7.34 (d, 1H) , 7.20 (m, 2H) , 7.11 (m, 2H) , 5.16 (d, 1H) , 4.87 (d, 1H) , 4.03 (dd, 1H) , 3.96 (d, 1H) , 3.74 (tt, 1H) , 3.34 (m, 2H (obscurecido por agua)) , 2.80- 3.05 (m, 6H) , 2.07 (br d, 1H) 1.90 (m, 3H) , 1.45- 1.66 (m, 4H) , 1.26 (m, 1H) , 0.89 (t, 3H) , 0.78 (t, 3H) .

Ejemplo 105

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- ({1- [2- metoxi- etil]- 4- piperidinil}sulfonil) fenil]metil}- 2,5- piperazinadiona



Una solución de hidrocloruro (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- piperidinil- sulfonil) fenil]metil}- 2,5- piperazinadiona (Ej. 104) 150 mg, 0.26 mmol) en metanol se cargó sobre una columna de aminopropilo- SPE, lavando con metanol. La

concentración proporcionó (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- piperidinilsulfonil) fenil]metil}- 2,5- piperazinadiona como un aceite verde (131 mg, 93%) .

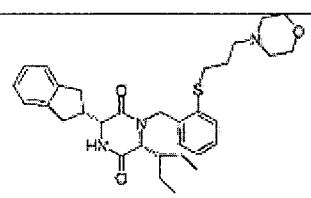
HPLC (A) Rt = 2.66 minutos; m/z $[M+H]^+$ =538

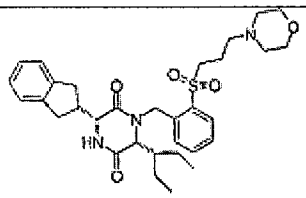
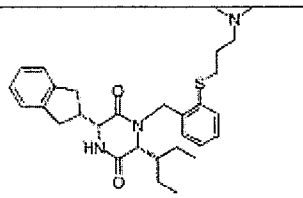
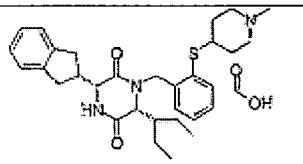
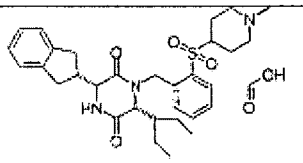
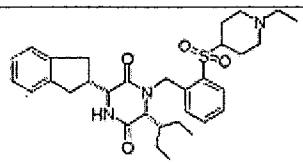
A una solución de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- piperidinilsulfonil) fenil]metil}- 2,5- piperazinadiona (131 mg, 0.24 mmol) en dimetilformamida (0.6 ml) se agregó carbonato de potasio (40 mg, 0.29 mmol) , 2- bromoetilmetiléter (22.6 µL, 0.24 mmol) y tetrabutilamonioyoduro (18 mg, 0.05 mmol) . La reacción fue calentada a 50°C durante 3 horas. Se agregó más 2- bromoetilmetileter (22.6 µL, 0.24 mmol) , tetrabutilamonioyoduro (18 mg, 0.05 mmol) y carbonato de potasio (40 mg, 0.29 mmol) y la reacción fue calentada a 50°C durante 1 hora. La reacción se cargó sobre una columna SCX- SPE, se lavó con metanol, luego fue eluida con 2M amoniaco/metanol. La concentración proporcionó (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- ({1- [2- metoxi- etil]- 4- piperidinil}sulfonil) fenil]metil}- 2,5- piperazinadiona como un aceite claro (117 mg, 82%) .

HPLC (A) Rt= 2.72 minutos, m/z $[M+H]^+$ =596

^1H NMR ($CDCl_3$) δ 8.05 (d, 1H) , 7.6 (t, 1H) , 7.5 (t, 1H) , 7.35- 7.2 (m, 5H) , 6.5 (br s, 1H) , 5.35 (d, 1H) , 4.95 (d, 1H) , 4.15 (dd, 1H) , 4.05 (d, 1H) , 3.5 (m, 2H) , 3.35 (s, 3H) , 3.2- 2.95 (m, 7H) , 2.85 (m, 1H) , 2.58 (m, 2H) , 2.05- 1.8 (m, 6H) , 1.75- 1.5 (m, 4H) 1.33 (m, 1H) , 0.95(t, 3H) , 0.85 (t, 3H) .

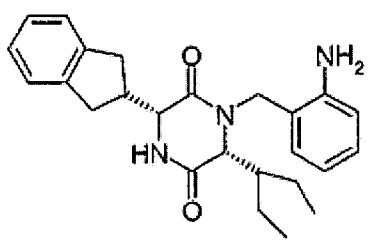
Los Ejemplos 106- 111 se prepararon mediante métodos análogos a aquel descrito para el intermedio 21 (azufres) e intermedio 22 (sulfones)

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
106		549.7	2.79 (A)	550;	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- {[3- (4- morfolinil) - propil]tio}fenil) metil]- 2,5- piperazinadiona.

107		581.7	2.74 (A)	582; 580	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- {[3- (4- morfolinil) - propil]sulfonil}fenil) metil]- 2,5- piperazinadiona.
108		507.7	2.71 (A)	508; 506	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- (dimetilamino) - propil]tio}fenil) metil]- 6- (1- etil- propil) - 2,5- piperazinadiona.
109		565.7	2.81 (A)	520; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metil- 4- piperidinil) tio]fenil}- metil) - 2,5- piperazinadiona. Formato
110		597.7	2.71 (A)	552; 549	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 6- (1- etilpropil) - 1- ({2- [(1- metil- 4- piperidinil) sulfonil]fenil}- metil) - 2,5- piperazinadiona. Formato
111		565.8	2.70 (A)	566; 564	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(1- etil- 4- piperidinil) sulfonil]fenil}- metil) - 6- (1- etilpropil) - 2,5- piperazinadiona. Formato

Ejemplo 112

(3R, 6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona



Una solución de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- nitrobenzil) - piperazina - 2,5- diona (Ex. 63) (1.99g, 4.57 mmol) en etanol (36 ml) se hidrogenó a temperatura ambiente y presión sobre 10% Pd/carbon (707 mg) durante 2.5 horas. La reacción fue filtrada a través de Celite y el solvente se removió al vacío para proporcionar

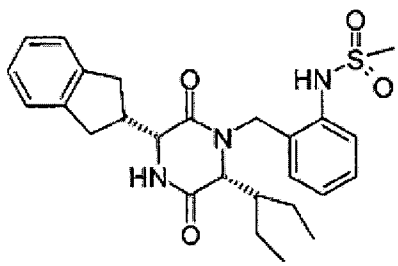
(3R, 6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazina- diona como un sólido marrón claro (1.79 g, 97%) .

HPLC (A) Rt= 3.34 minutos, m/z $[M+H]^+$ =406/407

^1H NMR ($CDCl_3$) δ 7.25 (m, 1H) , 7.18 (m, 3H) , 7.13 (dt, 1H) , 7.05 (dd, 1H) , 6.68 (m, 3H) , 5.45 (d, 1H) , 4.29 (br s, 2H) , 4.07 (dd, 1H) , 4.03 (d, 1H) , 3.91 (d, 1H) , 3.14 (m, 3H) , 2.93 (m, 1H) , 2.76 (m, 1H) , 1.88 (m, 1H) , 1.67 (m, 2H) , 1.25 (m, 2H) 1.00 (t, 3H) , 0.94(t, 3H) .

Ejemplo 113

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona- 1- piperazinil]metil}fenil) metanosulfonamida



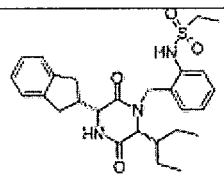
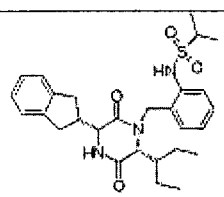
A una solución de (3R, 6R) - 1- [(2- aminopropil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (Ej. 112) (150 mg, 0.37 mmol) en diclorometano seco (2.5 ml) a 0°C se agregó trietilamina (0.26 ml) y 4- dimetilaminopiridina (450μg) . Después de cinco minutos se agregó cloruro de mesilo (34 μl, 0.74 mmol) y la reacción se agitó a temperatura ambiente hasta que se detecto ausencia del material de inicio mediante LCMS. La reacción fue concentrada y el residuo disuelto en tetrahidrofurano (3.5 ml) y tratado con una solución de hidróxido de sodio 1M (0.7 mL) . Después de una hora la reacción fue neutralizada y extraída con acetato de etilo (5 ml) . La fase orgánica fue separada, secada (Na_2SO_4) y concentrada. El residuo se purificó mediante cromatografía de columna de sílice para proporcionar N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona- 1- piperazinil]metil}fenil) metanosulfonamida como un sólido blanco (111 mg, 62%) .

HPLC (A) Rt= 3.15 minutos, m/z $[M+H]^+$ =484

^1H NMR ($CDCl_3$) δ 9.2 (s, 1H) , 7.58 (d, 1H) , 7.39 (dt, 1H) , 7.25 (m, 1H) , 7.23- 7.13 (m, 5H) , 6.38 (br d, 1H) , 5.13 (d, 1H) , 4.19 (d, 1H) , 4.12 (d, 1H) , 4.06 (dd, 1H) , 3.18 (m, 3H) , 3.1 (s,

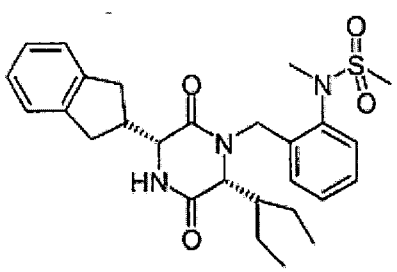
3H) , 2.90 (m, 1H) , 2.7 (m, 1H) , 1.84 (m, 1H) , 1.70 (m, 2H) 1.65 (m, 1H) , 1.35(m, 1H) , 1.09 (t, 3H) , 0.94 (t, 3H) .

Ejemplos 114- 115 se prepararon mediante métodos análogos a aquel descrito para el ejemplo 113.

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
114		497.6	3.25 (A)	449; 496	N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - etano- sulfonamida
115		511.6	3.5 (A)	512; 510	N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - 2- propanosulfonamida

Ejemplo 116

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona- 1- piperazinil]metil}fenil) - N- metilmetanosulfonamida



A una solución de N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona- 1- piperazinil]metil}fenil) metanosulfonamida (Ej. 113) (178 mg, 0.37 mmol) en dimetilformamida (1 mL) se agregó carbonato de potasio (102 mg, 0.74 mmol) seguido por yodometano (69 µl, 1.1 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas. La reacción fue apagada mediante adición de amoniaco en solución de metanol (2M, 0.74 ml) . Luego la reacción se diluyó con diclorometano (4 ml) y agua (4 ml) . La fase orgánica fue separada, pasada a través de una frita hidrofóbica y concentrada. El residuo se purificó mediante

cromatografía de columna de sílice para proporcionar N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona- 1- piperazinil]metil}fenil) - N- metilmetanosulfonamida como un sólido blanco (62 mg, 34%) .

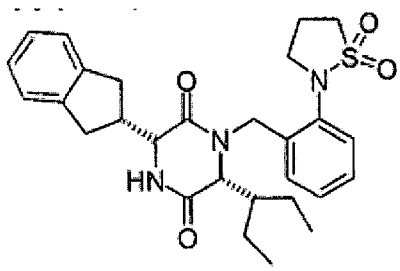
HPLC (A) Rt= 3.32 minutos, m/z $[M+H]^+$ =498

^{1}H NMR a temperatura ambiente mostró rotomeros claros los cuales coalescieron a 120°C para proporcionar el siguiente espectro:

^{1}H NMR (DMSO- d6, 120°C) δ 7.91 (br s, 1H) , 7.50 (m, 1H) , 7.36 (m, 2H) , 7.23 (m, 3H) , 7.15 (m, 2H) , 5.06 (d, 1H) , 4.43 (d, 1H) , 3.98 (dd, 1H) , 3.84 (d, 1H) , 3.22 (m, 3H) , 3.10- 2.98 (m, 8H) , 1.6- 1.28 (m, 5H) , 0.90- 0.8 (m, 6H) .

Ejemplo 117

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (1,1- dioxido- 2- isotiazolidinil) - fenil]metil}- 6- (1- etilpropil) - 2,5- piperazinadiona



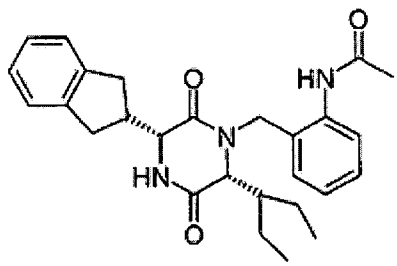
A una solución de (3R, 6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (Ej. 112) (130 mg, 0.32 mmol) en diclorometano (1.5 ml) a 0°C se agregó trietilamina (0.22ml) seguido por cloruro de sulfonilo 3- cloropropano (77 ul, 0.64 mmol) . Se agregó yoduro de amonio de tetrabutilo (1.2 mg) y la reacción se agitó a temperatura ambiente durante 18 horas. La reacción fue concentrada y el residuo se disolvió en etanol (1 ml) , se trató con trietilamina (0.11 ml) y se calentó a reflujo durante 5 horas. La reacción fue concentrada y el residuo se disolvió en diclorometano y lavó con agua. La fase orgánica fue recolectada a través de una frita hidrofóbica, concentrada y el residuo se purificó mediante cromatografía de columna de sílice para proporcionar (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (1,1- dioxido- 2- isotiazolidinil) - fenil]metil}- 6- (1- etilpropil) - 2,5- piperazinadiona como un sólido amarillo pálido (58 mg, 36%) .

HPLC (A) Rt = 3.3 minutos; m/z $[M+H]^+$ =510

^{1}H NMR (DMSO- d6, 120°C) δ 7.51 (d, 1H) , 7.35 (m, 3H) , 7.12 (m, 5H) , 5.28 (d, 1H) , 4.31 (d, 1H) , 4.06 (m, 2H) , 3.69 (m, 2H) , 3.37 (m, 2H) , 3.15 (m, 3H) , 2.93 (m, 1H) , 2.79 (m, 1H) , 2.57 (m, 2H) , 1.77 (m, 1H) , 1.64 (m, 3H) , δ 1.3 (m, 1H) , 0.95 (m, 6H) .

Ejemplo 118

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) acetamida GSK681884A R11351/189/1



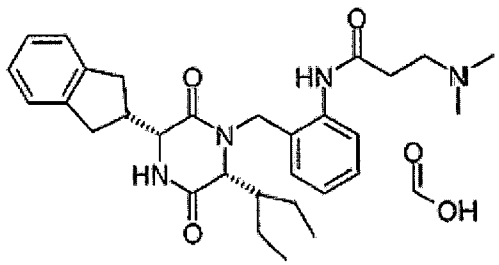
A una solución de (3R, 6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (Ej. 112) (70mg, 0.17mmol) en diclorometano anhidro (1ml) bajo una atmósfera de nitrógeno se agregó piridina (32ul) y cloruro de acetilo (14.7 ul) . Después de agitar durante 16 horas la mezcla de reacción fue particionada entre diclorometano y agua. Las fases fueron separadas mediante una frita hidrofóbica y la fase orgánica se cargó sobre un cartucho SCX- SPE 2g y se eluyo con metanol. La evaporación del metanol al vacío y el secado por congelamiento a partir de dioxano proporcionó N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) acetamida como un liofilato blanco (42mg) .

HPLC (A) Rt = 3.21 minutos; m/z $[M+H]^+$ =448

^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1H) , 8.28 (d, 1H) , 7.37 (t, 1H) , 7.27 (t, 1H) , 7.20 (m, 4H) , 7.07 (t, 1H) , 6.85 (s, 1H) , 5.25 (d, 1H) , 4.16 (d, 1H) , 4.04 (m, 1H) , 4.01 (d, 1H) , 3.15 (m, 3H) , 2.91 (m, 1H) , 2.78 (m, 1H) ; 2.26 (s ,3H) ; 1.88 (m, 1H) ; 1.70 (m, 2H) ; 1.56 (m, 1H) , 1.31 (m, 1H) ; 1.1 (t, 3H) ; 0.96 (t, 3H) .

Ejemplo 119

N^1- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - N^3, N^3- dimetil- β- alaninamida formato

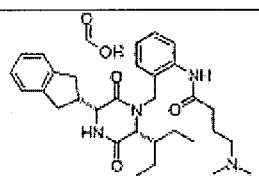


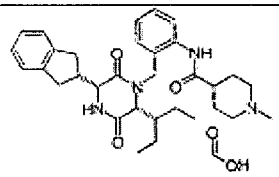
A una solución de (3R, 6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (Ej. 112) (70mg, 0.17mmol) en diclorometano anhidro (1ml) bajo una atmósfera de nitrógeno se agregó piridina (32ul) e hidrocloruro de N,N- dimetil- β- alanil- cloruro (36mg) . Después de agitar durante 16 horas la mezcla de reacción fue particionada entre diclorometano y agua. Las fases fueron separadas mediante una frita hidrofóbica y la fase orgánica se cargó sobre un cartucho SCX- SPE 2g y se eluyó con metanol, luego con amoniaco 1N en metanol. La fracción básica se evaporó al vacío y el residuo se purificó adicionalmente utilizando el sistema de cromatografía autoprep *(mass directed)* . El secado por congelamiento a partir de dioxano proporcionó formato de N^1- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - N^3, N^3- dimetil- β- alaninamida como un liofilato blanco (42mg) .

HPLC (A) Rt = 2.60 minutos; m/z $[M+H]^+$ =505

^{1}H NMR ($CDCl_3$) δ 10.14 (s, 1H) , 8.05 (d, 2H) , 7.33 (t, 1H) , 7.30 – 7.14 (m, 5H) , 7.10 (t, 1H) , 6.47 (s, 1H) , 5.16 (d, 1H) , 4.08 (m, 3H) , 3.15 (m, 3H) , 2.934 (m, 1H) , 2.80 (m, 3H) , 2.67 (t, 2H) , 2.40 (s, 6H) , 1.83 (m, 2H) ; 1.68 (m ,2H) ; 1.57 (m, 1H) ; 1.03 (t, 3H) ; 0.92 (t, 3H) .

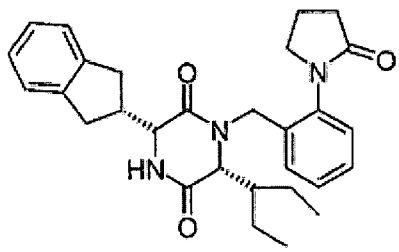
Ejemplos 120- 121 se prepararon mediante métodos análogos a aquel descrito para el ejemplo 119

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
120		518.7	2.62 (A)	519; 517	N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- fenil) - 4- (dimetil- amino) butanamida formato

121		530.7	2.64 (A)	531; 529	N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- fenil) - 4- piperidinacarboxamida formato

Ejemplo 122

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (2- oxo- 1- pirrolidinil) - fenil]metil}- 2,5- piperazinadiona



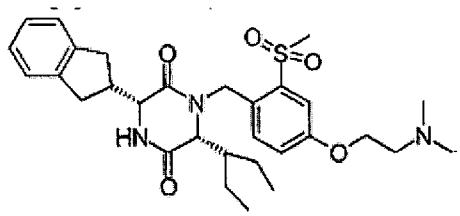
Se agregó de manera secuencial a un tubo microondas de 2 ml carbonato potásico (126mg) , yoduro cuproso (18mg) , (1R, 2R) - (-) - N, N`- dimetil- ciclohexano- 1,2- diamina (48mg) , 2- pirrolidinona (62mg) y (3R, 6R) - 1- [(2- bromofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (Ej. 30) (200mg, 0.42 mmol) y dioxano (0.4ml) . La mezcla fue calentada con agitación a 150°C durante 4000segundos en un microondas (Emrys™ Optimizer) . La mezcla de reacción fue diluida con diclorometano y se purificó sobre un cartucho SPE (5g , sílice) eluyendo con metanol: diclorometano (0 a 3%) . Las fracciones relevantes fueron evaporadas al vacío y se purificaron adicionalmente en un cartucho SCX- SPE de 2g eluyendo con diclorometano y luego con metanol. La evaporación del metanol al vacío y secado por congelamiento a partir de dioxano proporcionó (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (2- oxo- 1- pirrolidinil) - fenil]metil}- 2,5- piperazinadiona como un liofilato blanco (27 mg) .

HPLC (A) Rt = 3.14 minutos; m/z $[M+H]^+$ =474

^{1}H NMR ($CDCl_3$) δ 7.3 (m, 3H) , 7.20 (m, 3H) , 7.14 (m, 2H) , 5.18 (d, 1H) , 4.05 (d, 1H) , 4.04 (d, 1H) , 3.94 (d, 1H) , 3.83 (m, 1H) , 3.75 (m, 1H) , 3.12 (d, 3H) , 2.86 (m, 2H) , 2.58 (t, 2H) , 2.25 (m, 3H) , 1.71 (m, 1H) ; 1.59 (m ,3H) ; 1.29 (m, 1H) ; 0.92 (t, 3H) ; 0.88 (t, 3H) .

Ejemplo 123

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[4- (dimetilamino) etil]oxi}- 2- (metilsulfonil) fenil]metil}- 6- (1- etilpropil) - 2,5- piperazinadiona

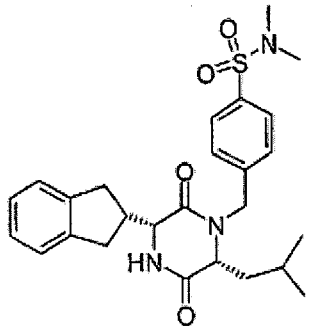


Se disolvió 2- {[4- (aminometil) - 3- (metilsulfonil) fenil]oxy}- N,N- dimetiletanamina (Int. 11) (0.42g) y 2- etilbutanal (0.20 mL) en 2,2,2- trifluoroetanol (10mL) . Luego se agregó trietilamina (0.20 mL) , y la mezcla se agitó durante la noche, luego se agregó ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}amino) etanóico (0.45g) y 4- clorofenilisonitrilo y la mezcla se agitó durante 3 días. La mezcla se disolvió en metanol a 0°C y se agregó cloruro de acetilo (1.7 mL) . Luego la mezcla se agitó durante 1 hora, pero LCMS no mostró pérdida del grupo Boc, entonces se agregó cloruro de acetilo (1.7 ml adicionales) y la solución fue agitada durante la noche. La mezcla fue concentrada bajo presión reducida y disuelta en cloroformo (20 mL) . Esta solución fue agitada con carbonato de hidrogeno de sodio (20ml) durante 1 hora. La fase orgánica fue separada y la fase acuosa extraída dos veces con cloroformo. Los extractos orgánicos fueron concentrados bajo presión reducida luego disueltos nuevamente en cloroformo (20 mL) . Se agregó ácido acético (12 mL) y la mezcla se agitó durante la noche. La mezcla se concentró bajo presión reducida para proporcionar un sólido amarillo el cual se purifico utilizando un cartucho SPE seguido por cromatografía autoprep *(mass directed)* y finalmente mediante HPLC de fase- inversa para proporcionar el compuesto del titulo como un sólido

^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1H) , 7.46 (d, 1H) , 7.41 (s, 1H) , 7.24- 7.14 (m, 4H) , 6.89 (s, 1H) , 5.11 (d, 1H) , 4.51- 4.41 (m, 2H) , 4.26 (d, 1H) , 4.07- 3.95 (m, 2H) , 3.72- 3.46 (m, 2H) , 3.18- 3.04 (m, 5H) , 2.98 (s, 6H) , 2.94- 2.73 (m, 3H) , 1.76- 1.52 (m, 4H) ; 1.43- 1.30 (m ,1H) ; 1.00- 0.87 (m, 6H)

Ejemplo 124

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N,N- dimetilbencenosulfonamide

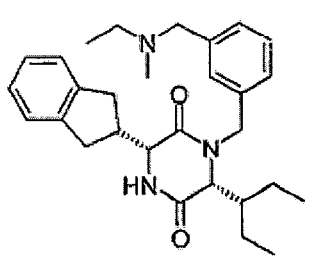


A una solución de 4- (aminometil) - N,N- dimetilbencenosulfonamida (467 mg) en metanol se agregó ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}amino) etanóico (640mg) , isocianuro de 2- {[(1,1- dimetiletil) (dimetil) silil]oxi}- fenilo (515 mg) y luego 3- metilbutanal (0- 24 ml) . La reacción luego se agitó durante 18 horas. Luego la reacción fue enfriada a 0°C y tratada con cloruro de acetilo (0.94 ml) y se dejo calentar a temperatura ambiente durante la noche. La reacción fue concentrada y el residuo se particionó entre cloroformo (10 ml) y bicarbonato de sodio (10 ml) y se agitó a temperatura ambiente durante 72 horas. La fase orgánica se recolectó y la fase acuosa se extrajo con cloroformo adicional. Luego los orgánicos combinados fueron concentrados y el residuo disuelto en metanol y pasado a través de SCX SPE y eluyendo en metanol. El metanol fue concentrado para proporcionar un residuo el cual se purifico mediante columna Redisep de (12g) para proporcionar el compuesto del titulo como un sólido amarillo, 290 mg.

LCMS (A) Rt = 3.24 minutos; m/z $[M+H]^+$ = 484; m/z $[M- H^-$ = 482

Ejemplo 125

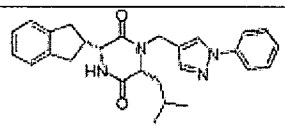
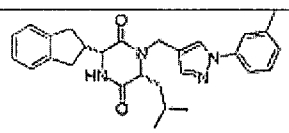
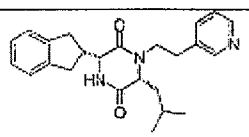
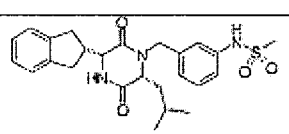
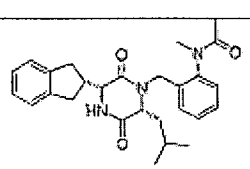
(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- {[etil(metil) amino]metil}fenil) - metil]- 6- (1- etilpropil) - 2,5- piperazinadiona

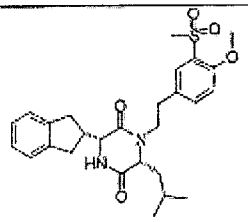


Una mezcla de N- {[3- (aminometil) fenil]metil}- N- metiletanamina (0.2 mmol) y 2- etilbutanal (0.2 mmol) en metanol (1ml) fue tratada con diisopropiletilamina (0.3 mmol) luego una solución de ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}amino) etanóico (0.2 mmol) en metanol (1 ml) y luego con una solución de isocianuro de 2- {[(1,1- dimetiletil) (dimetil) silil]oxi}- fenil (0.2 mmol) en metanol (1 ml) . Luego la reacción se agitó durante 2 días. La reacción luego se enfrió a 0°C y se trató con cloruro de acetilo (200 ul) y se dejo calentar a temperatura ambiente durante la noche. La reacción se concentro y el residuo se particionó entre cloroformo y bicarbonato de sodio y se calentó a 50°C durante 4 horas. El orgánico se recolectó y concentró y el residuo se purificó mediante HPLC Autoprep (10- 35% CH_3CH) . La concentración de las fracciones apropiadas proporcionaron el compuesto del titulo como una goma, 10.5 mg.

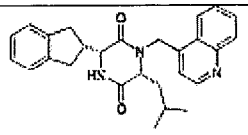
LCMS (A) Rt = 2.6 minutos; m/z $[M+H]^+$ = 462

Los siguientes ejemplos se prepararon mediante métodos análogos a aquel descrito para el ejemplo 124

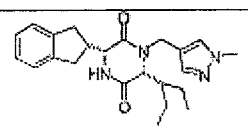
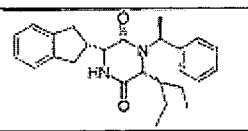
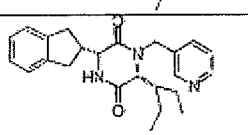
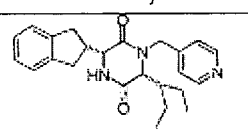
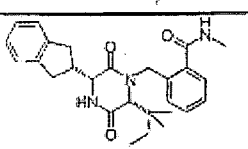
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
126		442.6	3.32 (A)	443; 441	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona.
127		456.6	3.44 (A)	457; 455	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[1- (3- metilfenil) - 1H- pirazol- 4- il]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona
128		391.5	2.61 (A)	392; 390	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (3- piridinil) etil]- 2,5- piperazinadiona
129		469.6	3.09 (A)	470; 468	N- (3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - metanosulfonamida
130		447.6	3.01 (A)	448; 446	N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - N- metilacetamida.

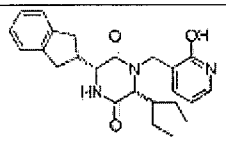
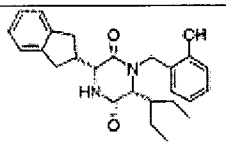
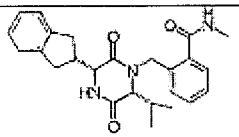
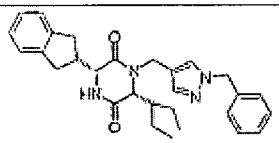
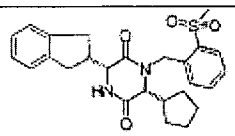
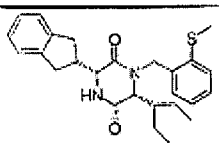
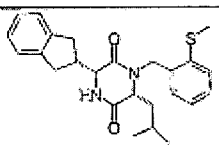
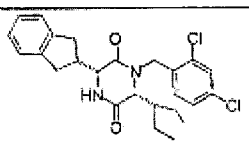
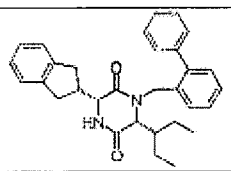
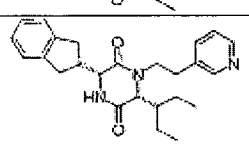
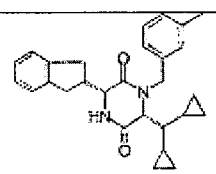
131		498.6	3.18 (A)	499; 497	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {2- [4- (metiloxi) - 3- (metilsulfonil) fenil]etil}- 6- (2- metilpropil) - 2,5- piperazinadiona

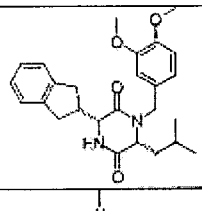
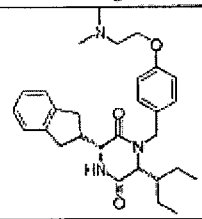
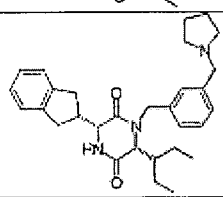
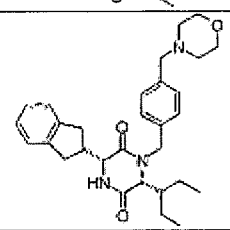
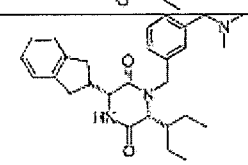
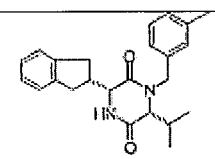
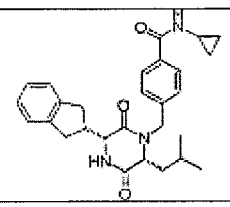
El siguiente ejemplo se preparó mediante un método análogo a aquel descrito para el ejemplo 125

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
132		427.5	3.1 (A)	428; 426	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (metilpropil) - 1- (4- quinolinilmetil) - 2,5- piperazinadiona.

Los siguientes ejemplos se prepararon mediante métodos análogos a aquel descrito para el ejemplo 1, opcionalmente con la adición de una base tal como trietilamina o DIPEA si se utilizaron sales de hidrocloruro de aminas.

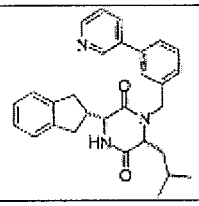
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
133		394.5	2.99 (A)	395; 393	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- metil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona.
134		404.5	3.62 (A)	405; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(S) - 1- feniletil] - 2,5- piperazinadiona
135		391.5	2.90 (A)	392; 390	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (3- piridinilmetil) - 2,5- piperazinadiona
136		391.5	2.90 (A)	392; 390	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (4- piridinilmetil) - 2,5- piperazinadiona
137		447.6	3.04 (A)	448; 446	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1,1- dimetilpropil) - 2,5dioxo- 1- piperazinil]metil}- N- metilbenzamida

138		407.5	2.91 (A)	408; 406	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- oxo- 1,2- dihidro- 3- piridinil) metil) - 2,5- piperazinadiona
139		406.5	3.5 (A)	407; 405	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- hidroxifenil) metil]- 2,5- piperazinadiona
140		419.5	2.85 (A)	420; 418	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 2,5dioxo- 1- piperazinil]metil}- N- metilbenzamida
141		470.6	3.42 (A)	471; 515	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[1- (fenilmetil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona
142		466.6	3.24 (A)	467; 465	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1{[2- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona
143		436.6	3.51	437; no vist o	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]metil}- 2,5- piperazinadiona
144		422.6	3.6	423; 421	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metiltio) fenil]metil}- 2,5- piperazinadiona
145		459.4	3.42 (D)	459	(3R, 6R) - 1- [(2,4- diclorofenil) - metil- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
146		466.6	3.79 (A)	467	(3R, 6R) - 1- (2- bifenililmetil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona
147		405.5	2.78 (A)	406	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [2- (3- piridinil) etil]- 2,5- piperazinadiona
148		428.6	3.55 (A)	429	(3R, 6R) - 6- (diciclopropilmetil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona

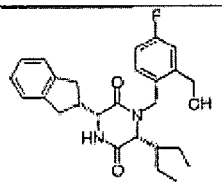
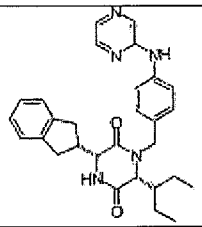
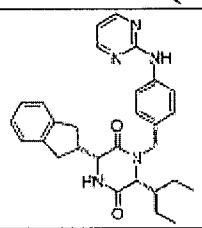
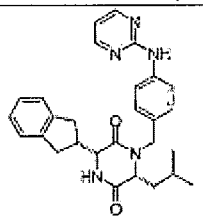
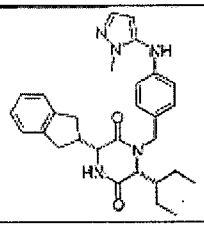
149		436.5	3.19 (A)	437	(3R, 6R) - 1- {[3,4- bis(metiloxi) - fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metil- propil) - 2,5- piperazinadiona
150		477.7	2.63 (A)	478	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1[(4- {[2- (dimetilamino) - etil]oxi}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona
151		473.7	2.69 (A)	474	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (1- pirrolidinilmetil) fenil]metil}- 2,5- piperazinadiona
152		489.7	2.51	490	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinilmetil) fenil]metil}- 2,5- piperazinadiona
153		447.6	2.57 (A)	448	ácido formico - (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({3- [(dimetilamino) metil]- fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona (1:1)
154		376.5	3.36 (A)	377	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona;
155		459.6	3.15 (A)	460	N- ciclopropil- 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

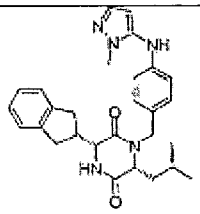
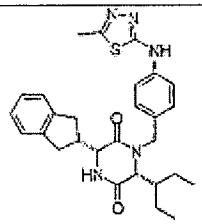
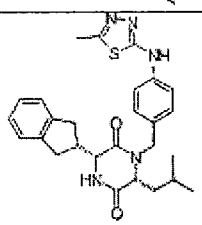
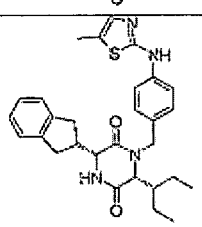
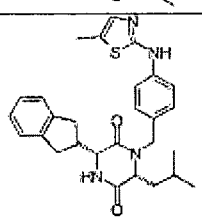
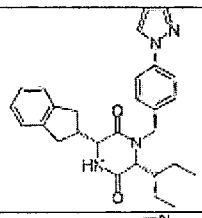
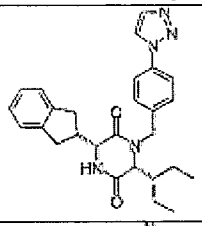
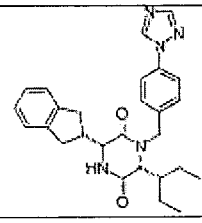
El siguiente ejemplo se preparó mediante un método análogo al ejemplo 125 empezando a partir del intermedio 12

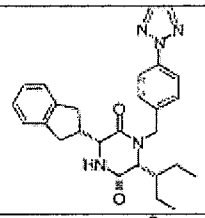
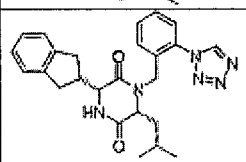
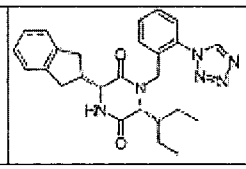
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre

156		453.6	3.2 (A)	454; 452	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metilpropil) - 1- {[3- (3- piridinil) fenil]- metil}- 2,5- piperazinadiona;

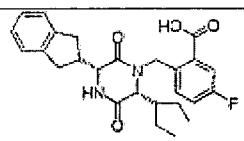
Los siguientes ejemplos se prepararon mediante métodos análogos a aquel descrito para el ejemplo1, utilizando los intermedios indicados, opcionalmente con la adición de una base tal como trietilamina o DIPEA si se utilizaron sales de hidrocloruro de aminas.

Ej. No.	Int. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
157	13		438.5	3.39 (A)	439; 484	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluoro- 2- (hidroximetil) - fenil]- metil}- 2,5- piperazinadiona;
158	23		483.6	0.81 (B)	484	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (pirazin- 2- il) aminofenil]- metil}- 2,5- piperazinadiona;
159	24		483.6	0.8 (B)	484	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (pirimid- 2- il) aminofenil]- metil}- 2,5- piperazinadiona;
160	24		469.6	0.78 (B)	470	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (pirimid- 2- il) aminofenil]- metil}- 2,5- piperazinadiona;
161	25		485.6	0.74 (B)	486	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(1- metil- 1H- pirazol- 5- il) amino]fenil}metil) - 2,5- piperazinadiona;

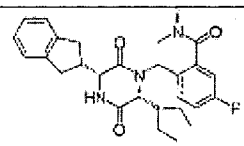
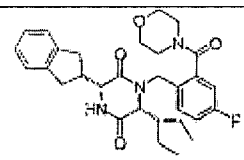
162	25		471.6	0.72 (B)	472	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- ({4- [(1- metil- 1H- pirazol- 5- il) amino]fenil}metil) - 2,5- piperazinadiona;
163	26		503.7	0.78 (B)	504	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (5- metil- 1,3,4- tiadiazol- 2- il) aminofenil]metil}- 2,5- piperazinadiona;
164	26		489.6	0.76 (B)	490	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (5- metil- 1,3,4- tiadiazol- 2- il) aminofenil]metil}- 2,5- piperazinadiona;
165	27		502.7	0.73 (B)	503	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (5- metil- 1,3,- tiazol- 2- il) aminofenil]metil}- 2,5- piperazinadiona;
166	27		488.7	0.69 (B)	489	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4[(5- metil- 1,3,- tiazol- 2- il) aminofenil]metil}- 2,5- piperazinadiona;
167	32		456.6	0.87 (B)	457	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1H- pirazol- 1- il) fenil]metil}- 2,5- piperazinadiona;
168	30		457.6	0.79 (B)	458	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1H- 1,2,3- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona
169	33		457.6	0.78 (B)	458	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1H- 1,2,4- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

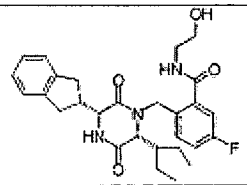
170	31		457.6	0.88 (B)	458	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (2H- 1,2,3- triazol- 2- il) fenil]metil}- 2,5- piperazinadiona;
171	37		444.5	0.76 (B)	445	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (1H- tetrazol- 1- il) fenil]metil}- 2,5- piperazinadiona;
172	37		458.6	0.76 (B)	459	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- tetrazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

El ejemplo 173 se preparó a partir del ejemplo 157 mediante métodos análogos a aquellos descritos para el intermedio 51 y ejemplo 65, sin aislamiento del aldehído intermedio

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
173		452.5	3.6 (A)	453; 451	ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluorobenzoico;

Los siguientes ejemplos se prepararon a partir del ejemplo 173 mediante métodos análogos a aquel descrito para el ejemplo 66, excepto utilizando diisopropilamina como la base en lugar de trietilamina.

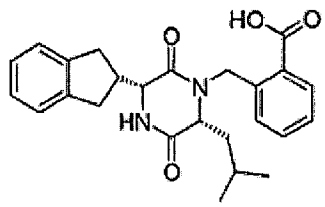
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
174		479.5	3.34 (A)	480; 424	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluoro- N,N- dimetilbenzamida;
175		521.6	3.25 (A)	522 566	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluoro- 2- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

176		495.5	2.96 (A)	496 494	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluoro- N- (2- hidroxietil) benzamida;

201

Ejemplo 177

Ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico



Se agitó (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (hidroximetil) fenil]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona (Int. 14) (1.488 g, 3.66 mmol) en acetonitrilo (8 ml) , agua (12 ml) y acetato de etilo. Se agregó peryodato de sodio (3.21g, 15 mmol) a la mezcla agitada seguido por hidrato de tricloruro de rutenio(3+) (24mg) . La mezcla se agitó vigorosamente durante 2.75 horas antes de ser filtrada y el residuo se lavó con acetato de etilo. El filtrado y los lavados fueron combinados y las fases separadas. La fase acuosa fue extraída con acetato de etilo (2x10 ml) . Las fases orgánicas fueron combinadas, secadas ($mgSO_4$) y evaporadas para dejar una espuma marrón (1.64 g) . La espuma marrón (1.63 g) fue agitada en acetonitrilo (150 ml) y se agregó por goteo a una solución de ácido sulfámico (426 mg, 4.38 mmol) en agua (15 ml) , seguido después de 3 minutos mediante la adición por goteo de una solución de cloruro de sodio (430 mg, 4.75 mmol) en agua (15 ml) luego de agitar la mezcla a temperatura ambiente durante 2 horas esta se dejo sentar a temperatura ambiente durante la noche (16.33 horas) antes de ser evaporada bajo presión reducida para remover el solvente orgánico. El residuo acuoso se particionó entre acetato de etilo (100ml) y agua (10ml) . La fase orgánica fue lavada con una solución de cloruro de sodio acuoso saturado (25 ml) , secada ($MgSO_4$) , evaporada bajo presión reducida y secada al vacío para proporcionar ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico como una espuma anaranjada/ marrón (1.608g) . Una porción de Ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6-

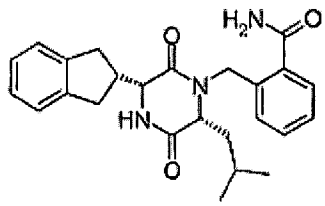
(2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico se purificó adicionalmente mediante cromatografía autoprep *(mass directed)* para proporcionar un sólido blanco (45 mg) .

LCMS (A) Rt = 3.22 minutos; m/z $[M+H]^+$ = 421

^1H NMR ($CDCl_3$) δ 8.36 (br s, 1H) , 8.05 (d, 1H) , 7.55 (t, 1H) , 7.39 (t, 1H) , 7.33 (d, 1H) , 7.22 (m, 2H) , 7.16 (m, 2H) , 5.49 (d, 1H) , 4.71 (d, 1H) , 4.14 (dd, 1H) , 3.93 (dd, 1H) , 3.14 (m, 3H) , 2.90 (m, 2H) , 1.93 (m, 1H) ; 1.82 (m ,1H) ; 1.71 (m, 1H) , 0.91 (t, 6H) .

Ejemplo 178

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida



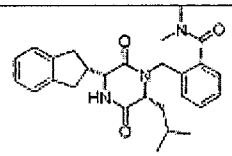
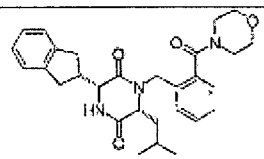
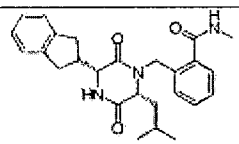
Se disolvió ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico (ej. 177) (600 mg, 1.26 mmol) en diclorometano seco (9 ml) y trietilamina (353.4 ul, 2.53 mmol) bajo nitrógeno. Se agregó tetrafluoroborato de 2- (1H- benzotriazol- 1- il) - 1,1,3,3- tetrametiluronio 8488 mg, 1.52 mmol) a la mezcla, la cual se agitó durante 6 horas a temperatura ambiente antes de dividirse en 4 y cada porción se trató con una amina.

A una porción se agregó una solución de amoniaco 2M en metanol (1 ml, 2 mmol) . La mezcla fue dejada sentar a temperatura ambiente durante el fin de semana, antes de ser diluida con diclorometano (2ml) y lavada con ácido clorhídrico 1M (2ml) seguido por una solución de bicarbonato de sodio acuoso saturado (2 ml) . Las fases fueron separadas utilizando una frita hidrofóbica y la fase orgánica se purgó bajo nitrógeno para dejar una espuma de color marrón. La espuma fue purificada mediante cromatografía autoprep *(mass directed)* para proporcionar 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida como un sólido blanco.

LCMS (A) Rt = 2.94 minutos; m/z $[M+H]^+$ = 420

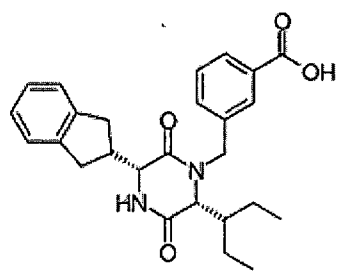
^{1}H NMR ($CDCl_3$) δ 8.15 (br s, 1H) , 7.47 (d, 1H) , 7.38 (br t, 1H) , 7.31 (d, 1H) , 7.24 (t, 1H) , 7.16 (m, 4H) , 6.77 (br s, 2H) , 5.42 (d, 1H) , 4.28 (d, 1H) , 4.03 (m, 1H) , 3.91 (m, 1H) , 3.06 (m, 3H) , 2.82 (m, 2H) , 1.92 (m, 1H) ; 1.73 (m ,2H) ; 0.93 (d, 6H) .

Los siguientes ejemplos se prepararon mediante métodos análogos a aquel descrito para el ejemplo 178

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
179		477.6	3.08 (A)	448; 446	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbenzamida;
180		489.6	3.08 (A)	490; 488	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;
181		433.6	3.00 (A)	434; 432	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

Ejemplo 182

Ácido 3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico

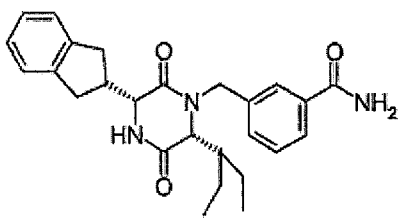


Se disolvió 3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoato de 1,1- dimetiletilo (Int. 15) (518 mg, 1.05 mmol) en ácido clorhídrico 2M en éter (2ml) y se dejo sentar a temperatura ambiente durante la noche (18.25 horas) . Luego se agregó ácido clorhídrico 4M en dioxano (1 ml) a la mezcla, la cual se dejo sentar 47 horas adicionales antes de agregar mas ácido clorhídrico 4M en dioxano (0.4 ml) .

Después de 5.5 horas adicionales la mezcla fue evaporada bajo presión reducida para dejar una espuma. La espuma se disolvió en ácido clorhídrico 4M en dioxano (1 ml) y se dejo sentar durante la noche (22.33 horas) antes de ser evaporada bajo presión reducida para dejar una goma, la cual fue evaporada a partir de ciclohexano y secada al vacío para proporcionar el ácido 3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico como una espuma de color marrón pálido (540 mg) .
LCMS (A) Rt = 3.3 minutos; m/z $[M+H]^+$ = 435

Ejemplo 183

3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida



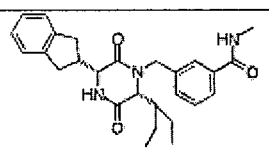
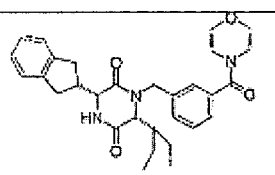
Se disolvió ácido 3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzóico (ej. 182) (493 mg, 0.96 mmol) en diclorometano seco (9 ml) bajo nitrógeno y se agregó trietilamina (267.2 ul, 1.92 mmol) . Después de 5 minutos se agregó tetrafluoroborato de 2- (1H- benzotriazol- 1- il) - 1,1,3,3- tetrametiluronio (369 mg, 1.15 mmol) a la mezcla, la cual se agitó durante 2 horas antes de dejarse sentar a temperatura ambiente durante la noche (18.25 horas) y luego se dividió en 3 partes y cada porción fue tratada con una amina.

A una porción se agregó una solución de amoniaco 2M en metanol (1 ml, 2 mmol) . La mezcla fue dejada sentar a temperatura ambiente durante 5 horas, antes de ser diluida con diclorometano (3ml) y lavada con ácido clorhídrico 1M (1ml) seguido por una solución de bicarbonato de sodio acuoso saturado (2 ml) . Las fases fueron separadas utilizando una frita hidrofóbica y la fase orgánica se purgó bajo nitrógeno para dejar una espuma de color marrón. La espuma fue purificada mediante cromatografía autopreparativa para proporcionar 3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida como una espuma de color marrón pálido (80 mg, 56%)

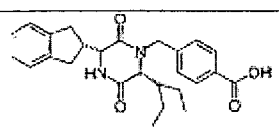
LCMS (A) Rt = 3.01 minutos; m/z $[M+H]^+$ = 434

^{1}H NMR ($CDCl_3$) δ 8.01 (br s, 1H) , 7.74 (m, 2H) , 7.41 (m, 2H) , 7.18 (m, 4H) , 6.44 (br s, 2H) , 5.35 (d, 1H) , 4.10 (m, 2H) , 3.93 (d, 1H) , 3.14 (m, 3H) , 2.88 (m, 2H) , 1.73 (m, 1H) , 1.66 (m, 1H) , 1.58 (m, 2H) , 1.31 (m, 1H) ; 0.92 (t, 3H) , 0.87 (t,3H) .

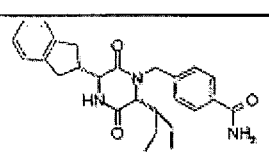
Los siguientes ejemplos se prepararon mediante métodos análogos a aquel descrito para el ejemplo 183

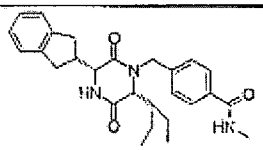
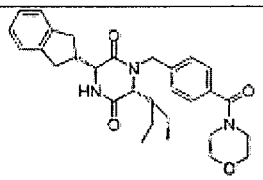
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
184		447.6	3.05 (A)	448; 446	3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida;
185		503.6	3.07 (A)	504; 502	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

El siguiente ejemplo se preparó a partir del intermedio 54 mediante un método análogo a aquel descrito para el ejemplo 182

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
186		434.5	3.27 (A)	435; 433	ácido 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico;

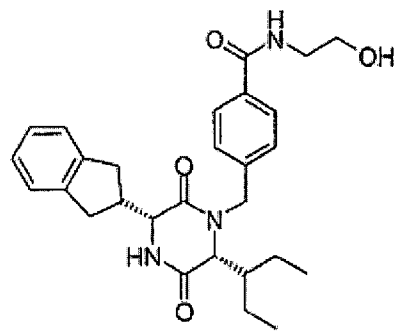
Los siguientes ejemplos se prepararon a partir del ejemplo 186 mediante métodos análogos a aquel descrito para el ejemplo 183

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
187		433.6	2.98 (A)	434; 432	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

188		447.6	3.16 (A)	448; 492	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida;
189		503.6	3.1 (A)	504; 502	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;

Ejemplo 190

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) benzamida



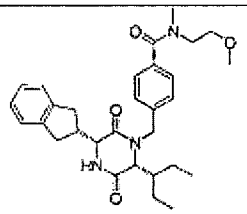
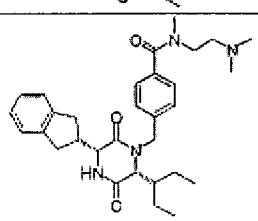
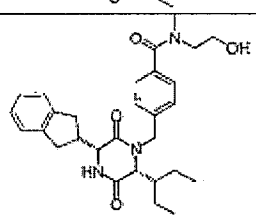
A una solución de los estereoisómeros mezclados del intermedio 49 (100 mg, 0.23° mmol) y 2-aminoetanol (30 uL, 0.460 mmol) en CH_2Cl_2 (2 mL) se agregó diisopropiletilamina (90 uL, 0.506 mmol) , hidrocloruro de 1- (3- dimetilaminopropil) - 3- etilcarboiimida (EDCL.HCl) (49 mg, 0.253 mmol) e hidrato de 1- hidroxibenzotriazol (HOBT) (6 mg, 0.046 mmol) . La mezcla de reacción se agitó a temperatura ambiente hasta ser juzgada completa mediante LCMS. A las16 horas, LCMS indicó conversión del 55% aproximadamente; por lo tanto se agregó 2-aminoetanol (10 µL, 0.153 mmol) . La mezcla de reacción se continúo agitando durante 4 días adicionales. LCMS indicó conversión del 65% aproximadamente. La reacción se diluyo con AtOAc. La solución resultante fue lavada con una solución de $NaHCO_3$ acuoso saturado y salmuera. Los orgánicos fueron secados sobre $MgSO_4$, filtrados y concentrados para proporcionar 80 mg de un sólido blanco. El residuo crudo se purificó mediante cromatografía rápida sobre gel de sílice [SCO, columna RediSep® de 4g, CH_2Cl_2 / MeOH 1%- 10%] para proporcionar 29 mg de 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5-

dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) benzamida (trans- isómero) como un aceite y 15 mg del ejemplo 190, 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) benzamida (cis- isómero) como un aceite.

HPLC (B) Rt = 0.71 minutos; m/z $[M+H]^+ = 478$

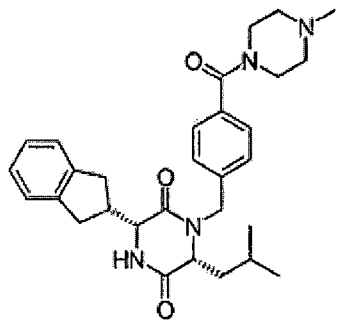
^1H NMR ($CDCl_3$) δ 7.76 (d, 2H) , 7.54 (d, 2H) , 7.30 – 7.15 (m, 2H) , 7.05 (t, 1H) , 5.67 (br s, 1H) , 5.33 (d, 1H) , 4.07 (m, 2H) , 3.89 (d, 1H) , 3.82 (t, 2H) , 3.62 (m, 2H) , 3.15 (m, 3H) , 3.0 – 2.75 (m, 2H) , 2.54 (br s, 2H) , 1.80- 1.50 (m, 4H) ; 1.34 (m, 1H) ,0.95 (t, 3H) , 0.88 (t,3H) .

Los siguientes ejemplos se prepararon a partir del intermedio 49 mediante métodos análogos a aquel descrito para el ejemplo 190.

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
191		505.7	0.78 (B)	506	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metil- N- [2- (metiloxi) etil]benzamida;
192		518.7	0.67 (B)	519	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (dimetilamino) etil]- N- metilbenzamida;
193		491.6	0.72 (B)	492	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) - N- metilbenzamida;

Ejemplo 194

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- [(4- metil- 1- piperazinil) crbonil]- fenil}- metil) - 6- (2- metilpropil) - 2,5- piperazinadiona



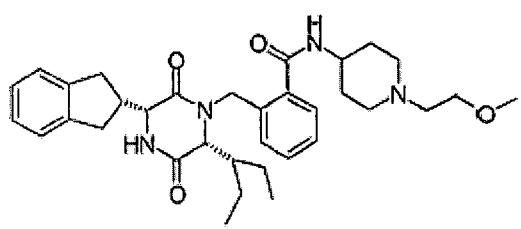
A una solución de los estereoisómeros mezclados del intermedio 50 (110 mg, 0.262 mmol) en CH_2Cl_2 (2.3 mL) se agregó diisopropiletilamina (55 µL, 0.288 mmol) y hexafluorofosfato (HATU) (119 mg, 0.314mmol) . Después de agitar a temperatura ambiente durante 2 horas, LCMS indicó conversión completa. La reacción fue diluida con EtOAc y lavada con una solución de $NaHCO_3$ acuoso saturado y salmuera. Los orgánicos fueron secados sobre $MgSO_4$, filtrados y concentrados para proporcionar 180 mg de un sólido blanco. El residuo crudo se purificó mediante cromatografía rápida de gel de sílice [SCO, columna RediSep® de 4g, CH_2Cl_2 / MeOH 1%- 10%] para proporcionar 23 mg de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- [(4- metil- 1- piperazinil) crbonil]- fenil}- metil) - 6- (2- metilpropil) - 2,5- piperazinadiona (trans- isómero) como un polvo blanco y 41 mg del ejemplo 193, (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- [(4- metil- 1- piperazinil) crbonil]- fenil}- metil) - 6- (2- metilpropil) - 2,5- piperazinadiona (cis- isómero) como un polvo blanco.

HPLC (B) Rt = 0.62 minutos; m/z $[M+H]^+$ = 503

^1H NMR ($CDCl_3$) δ 7.40 (d, 2H) , 7.32 (d, 2H) , 7.28- 7.15 (m, 4H) , 5.36 (d, 1H) , 4.07 (dd, 1H) , 3.94 (d, 1H) , 3.81 (m, 3H) , 3.47 (br s, 2H) , 3.12 (m, 3H) , 2.68 (m, 2H) , 2.60- 2.30 (m, 4H) , 2.36 (s, 3H) , 1.97 (m, 1H) , 1.83 (m, 1H) ; 1.66 (m, 1H) ,0.97 (t, 6H) .

Ejemplo 195

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- {1- [2- (metiloxi) etil]- 4- piperidinil}benzamida



A una solución agitada de 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- 4- piperidinilbenzamida (ejemplo 83) (101 mg, 0.2 mmol) en dimetilformamida anhidro (2 ml) se agregó carbonato de potasio 827 mg, 0.2 mmol) y 2- bromoetilmetiléter (20.2 uL, 0.21 mmol) . La reacción se agitó durante 20 horas. Se agregó adicionalmente carbonato de potasio 813.5 mg, 0.1 mmol) y 2- bromoetilmetil- éter (15 uL, 0.16 mmol) y la reacción se agitó durante 2.5 horas antes de agregar más 2- bromoetilmetiléter (15 uL, 0.16 mmol) . Luego la reacción se agitó a temperatura ambiente durante el fin de semana (71 horas) antes de agregar mas 2- bromoetilmetiléter (15 uL, 0.16 mmol) . Luego la reacción se agitó durante 25.5 horas antes de agregar adicionalmente carbonato potásico (16 mg, 0.11 mmol) y 2- bromoetilmetileter (15 uL, 0.16 mmol) y la reacción se agitó durante 18 horas. La mezcla de reacción se particionó entre diclorometano (10 ml) y cloruro de amonio acuoso saturado (5 ml) . La fase acuosa fue extraída con diclorometano (4 ml) . Las fases fueron separadas utilizando una frita hidrofóbica. La fase orgánica combinada fue evaporada bajo presión reducida para proporcionar un sólido de color anaranjado pálido. El sólido en un volumen pequeño de diclorometano se cargó sobre una columna SCX –SPE, se lavó con metanol, luego se eluyó con 2M amoniaco/metanol. La concentración proporcionó una espuma de color crema pálido, la cual se cargó sobre una columna de cromatografía rápida de sílice de 12g (pre- eluida con trietilamina al 0.4% en acetato de etilo) . La columna fue eluida con 0% a 100% solvente B en solvente A (solvente A= trietilamina al 0.4% en acetato de etilo, y solvente B = etanol al 20% en acetato de etilo) para proporcionar 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- {1- [2- (metiloxi) etil]- 4- piperidinil}benzamida como un sólido blanco (68 mg, 60%) .

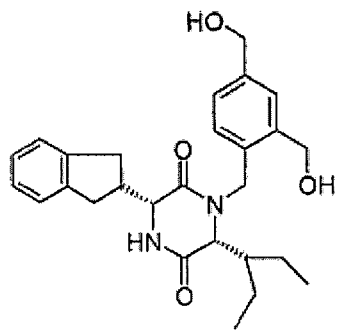
LCMS (A) Rt = 2.64 minutos; m/z $[M+H]^+$ = 575

^{1}H NMR ($CDCl_3$) δ 7.54 (br d, 1H) , 7.43 (br d, 1H) , 7.38 (br t, 1H) , 7.24 (d, 2H) , 7.17 (m, 3H) , 6.78 (d, 1H) , 5.11 (d, 1H) , 4.43 (d, 1H) , 4.12 (d, 1H) , 4.03 (dd, 1H) , 3.98 (m, 1H) , 3.52 (t, 2H) , 3.36 (s, 3H) , 3.11 (m, 3H) ; 2.92 (m, 3H) , 2.81 (m, 1H) , 2.59 (t, 2H) , 2.23 (m,2H) , 2.05 (m, 2H) , 1.77 – 1.53 (m, 6H) , 1.35 (m, 1H) , 0.96 (t, 3H) , 0.90 (t,3H) .

Ejemplo 196

(3R,6R) - 1- {[2,4- bis(hidroximetil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona

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Se disolvió [4- (aminoetil) benceno- 1,3- diil]dimetanol (2.22g, 13.3 mmol) y ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}amino) etanóico (3.87 g, 13.3 mmol) en 5 mL de metanol. Se agregó 2- etilbutanal (1.33 g, 13.3 mmol) en la solución. La solución resultante se agitó a temperatura ambiente durante 30 minutos. Luego se agregó isocianuro de 4- clorofenilo (1.44 g, 13.3 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. El solvente fue removido al vacío. El residuo se disolvió en 20 mL de cloroformo y se enfrió a 0°C. Luego la solución fría se trato con Hcl 4M en dioxano. Luego la mezcla resultante se calentó a temperatura ambiente durante la noche. Luego el solvente se removió y disolvió nuevamente en 150 mL cloroformo. Luego la solución se lavó con 30 mL de bicarbonato de sodio saturado. La solución acuosa fue extraída con 2 x 30 mL de cloroformo. Los orgánicos combinados se secaron sobre sulfato de magnesio y se concentraron. El residuo resultante se disolvió en 30 mL de cloroformo. La solución se trato con 1.5 mL de ácido acético y se agitó a temperatura ambiente durante la noche. Luego la solución se concentró. El residuo se purifico mediante cromatografía de gel de sílice eluyendo con acetato de etilo al 50- 100% en héxanos para proporcionar (3R,6R) - 1- {[2,4- bis(hidroximetil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona 81.05 g, 17%) como un sólido blancuzco.

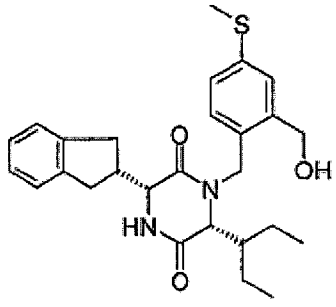
LCMS (B) Rt = 0.71 minutos; m/z $[M+H]^+$ = 451

^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1H) , 7.16- 7.27 (m, 5H) , 7.02 (s, 1H) , 5.45 (d, 1H) , 4.69 (d, 3H) , 4.66 (s, 2H) , 4.57 (d, 1H) , 4.10 (d, 1H) , 3.94- 4.05 (m, 2H) , 3.09- 3.13 (m, 2H) , 2.87- 2.89 (m, 1H) , 2.77- 2.80 (m, 1H) , 2.30 (bs, 3H) , 1.70- 1.80 (m, 1H) ; 1.51- 1.68 (m, 3H) , 1.20- 1.30 (m, 1H) , 0.80- 0.90 (m, 6H) .

Ejemplo 197

(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metilito) fenil]metil}- 2,5- piperazinadiona

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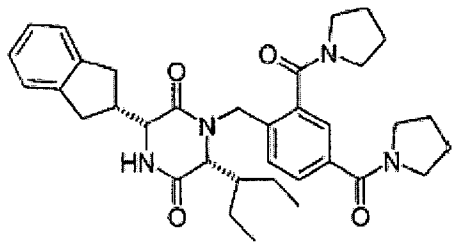
Se disolvió ácido (2R) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}amino) etanóico (0.80 g, 2.73 mmol) , [2- (aminometil) - 5- (metilito) fenil]metanol (0.50 g, 2.73 mmol) y 2- etilbutanal (0.36 mL, 2.73 mmol) en 10 mL de metanol. La solución resultante se agitó a temperatura ambiente durante 30 minutos. Luego se agregó isocianuro de 4- clorofenilo (0.30 g, 2.73 mmol) y la mezcla resultante se agitó a temperatura ambiente durante la noche. El solvente se removió al vacío. Luego el residuo se purificó mediante cromatografía de gel de sílice eluyendo con diclorometano al 10- 100% en héxanos para proporcionar [(1R) - 2- ((1- {[(4- clorofenil) amino]carbonil}- 2- etilbutil) {[2- etilbutil) {[2- (hidroximetil) - 4- (metilito) fenil]metil}amino) - 1- (2,3- dihidro- 1H- inden- 2- il) - 2- oxoetil]carbamato de 1,1- dimetiletilo como un sólido blanco. Este material (0.86 g, 1.24 mmol) se trató con hidrocloruro 4 M en solución de dioxano (12.4 ml, 2.48 mmol) a temperatura ambiente durante 2 horas, luego se colocó en un congelador a - 20°C durante 72 horas. Después se calentó a temperatura ambiente durante 2 horas. Luego el solvente se removió y disolvió nuevamente en 15 mL de cloroformo. Luego la solución se agitó con 10 mL de bicarbonato de sodio saturado durante 20 minutos. Las fases se separaron. La solución acuosa se extrajo con 2 x 15 mL de cloroformo. Los orgánicos combinados se secaron sobre sulfato de magnesio y se concentraron. El residuo resultante se disolvió en 15 mL de cloroformo. La solución se trato con 0.75 mL de ácido acético al 20% v/v en dioxano y se agito a temperatura ambiente durante la noche. Luego la solución se concentró. Luego el residuo se disolvió en 50 mL de acetato de etilo y se lavó con 15 mL de solución de bicarbonato de sodio. La fase orgánica se secó sobre sulfato de magnesio y se concentró. El residuo se purificó mediante cromatografía de gel de sílice eluyendo con acetato de etilo al 30- 70% en héxanos para proporcionar (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metiltio) fenil]metil}- 2,5- piperazinadiona como un sólido blanco. LCMS (D) Rt = 2.89 minutos; m/z $[M+H]^+$ = 467

^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1H) , 7.20- 7.35 (m, 3H) , 7.13- 7.17 (m, 3H) , 5.25 (d, 1H) , 4.61 (dd, 2H) , 4.36 (d, 1H) , 4.11- 4.13 (m, 1H) , 3.92 (d, 1H) , 3.09- 3.11 (m, 3H) , 2.88- 2.91 (m, 2H) , 2.50 (s, 3H) , 1.72- 1.82 (m, 1H) , 1.60- 1.65 (m, 3H) , 1.20- 1.35 (m, 1H) , 0.92 (t, 3H) , 0.89 (t, 3H) .

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Ejemplo 199

(3R,6R) - 1- {[2,4- bis(1- pirrolidinilcarbonil) fenil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona



Se disolvió ácido 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 1,3- bencenodicarboxílico (Int. 52) (50 mg, 0.105 mmol) , HATU (99.4 mg, 0.262 mmol) y pirrolidina (17.mg, 0.251 mmol) en 1 mL de diclorometano. Luego se agregó diisopropiletilamina (54.1 mg, 0.418 mmol) . La solución resultante se agitó a temperatura ambiente durante 1 hora. Luego la mezcla de reacción cruda se purificó mediante HPLC Gilson con ácido trifluoroacético al 0.1% en acetonitrilo /agua. Las fracciones conteniendo el producto se combinaron y concentraron. El residuo se disolvió en 20 ml de acetato de etilo, se lavó con 5 mL de bicarbonato de sodio saturado, se secó sobre $MgSO_4$ y concentró para proporcionar (3R,6R) - 1- {[2,4- bis(1- pirrolidinilcarbonil) fenil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (30 mg, 49%) como un sólido blanco.

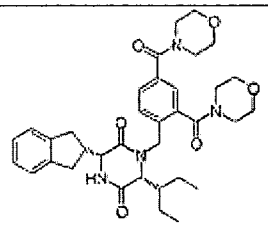
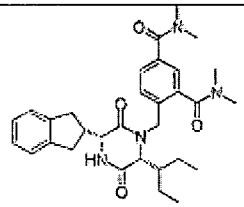
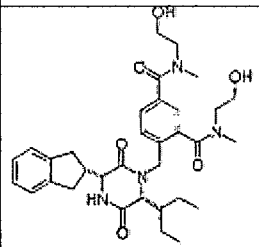
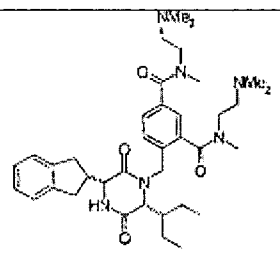
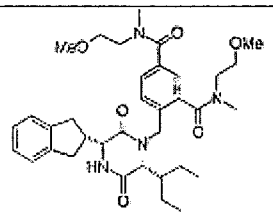
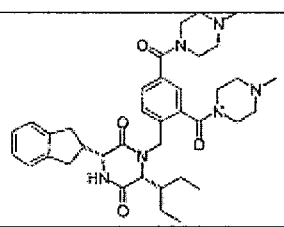
LCMS (B) Rt = 0.77 minutos; m/z $[M+H]^+$ = 585.4

^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1H) , 7.47 (s, 1H) , 7.29 (1, 1H) , 7.19 (m, 2H) , 7.14 (m, 2H) , 5.06 (d, 1H) , 4.24 (d, 1H) , 3.99 (s, 1H) , 3.97 (d, 1H) , 3.59 (t, 4H) , 3.36- 3.41 (m, 4H) , 3.06- 3.27 (m, 4H) , 1.80- 2.00 (m, 8H) , 1.48- 1.70 (m, 4H) , 1.20- 1.30 (m, 2H) , 0.80- 0.90 (m, 6H) .

Los siguientes ejemplos se prepararon mediante métodos análogos a aquel descrito para el ejemplo 199

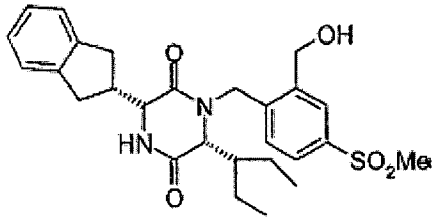
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre

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200		616.8	0.72 (B)	617	(3R, 6R) - 1- {[2,4- bis(4- morfolinilcarbonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;
201		532.7	0.73 (B)	533	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N,N`,N`- tetrametil- 1,3- bencenodicarboxamida;
202		592.7	0.66 (B)	593	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- bis(2- hidroxietil) - N,N´- dimetil- 1,3- bencenodicarboxamida;
203		646.9	0.58 (B)	647	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- bis[2- (dimetilamino) etil]- N,N´- dimetil- 1,3- bencenodicarboxamida;
204		620.8	0.75 (B)	621	4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- dimetil- N,N´- bis[2- (metiloxi) etil]- 1,3- bencenodicarboxamida;
205		641.9	0.57 (B)	643	(3R, 6R) - 1- {[2,4- bis(4- metil- 1- piperazinil) carbonil]fenil}]metil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

Ejemplo 206

(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2(hidroximetil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona



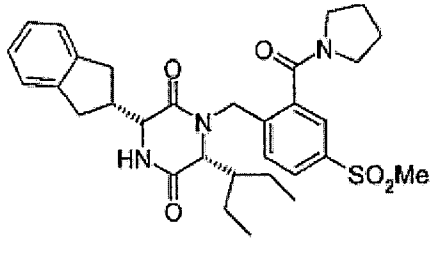
Se trató ((3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metilito) fenil]metil}- 2,5- piperazinadiona (ejemplo 197) (167 mg, 0.36 mmol) con peroxido de hidrógeno al 30% (0.16 mL, 1.44 mmol) y 1 mL de ácido acético a 80°C durante 6 horas. Luego el solvente se removió. El material crudo se modifico mediante cromatografía de columna de gel de sílice eluyendo con metanol al 0- 5% en diclorometano para proporcionar (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2(hidroximetil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona como un sólido blanco.

LCMS (B) Rt = 0.73 minutos; m/z $[M+H]^+$ = 499

^{1}H NMR (CD_3OD) δ 8.08 (S, 1H) , 7.92 (d, 1H) , 7.47 (d, 1H) , 7.19 (m, 2H) , 7.12 (m, 2H) , 5.28 (d, 1H) , 4.78 (dd, 2H) , 4.52 (d, 1H) , 4.41 (d, 1H) , 4.00 (d, 1H) , 3.26- 3.33 (m, 1H) , 3.16 (d, 1H) , 3.10- 3.16 (m, 1H) , 3.00 (dd, 2H) , 2.90 (dd, 1H) , 1.87 (m, 1H) , 1.66 (m, 3H) , 1.30- 1.41 (m, 1H) , 0.90- 1.00 (m, 6H) .

Ejemplo 208

(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) - 2- (1- pirrolidinilcarbonil) fenil]metil}- 2,5- piperazinadiona



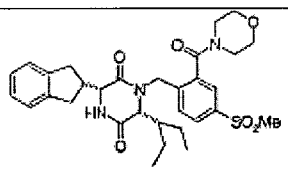
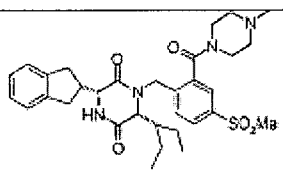
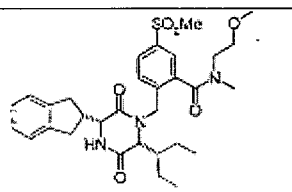
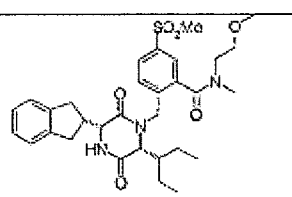
Se disolvió ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- (metilsulfonil) benzóico (Int. 53) (50 mg, 0.097 mmol) , HATU (48.0 mg, 0.126 mmol) y pirrolidina (16 µL, 0.194 mmol) en 1 mL de acetonitrilo. Luego se agregó diisopropiletilamina (34 µL, 0.194 mmol) . La solución resultante se agitó a temperatura

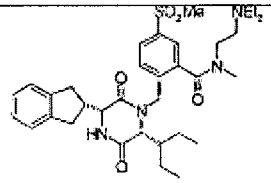
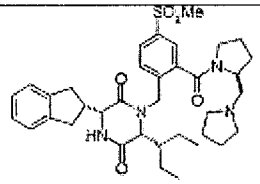
ambiente hasta que LCMS no monotoreó más material de inicio. Luego la mezcla de reacción cruda se purificó mediante HPLC Gilson eluyendo con ácido trifluorocetico al 0.1% en acetonitrilo/agua. Las fracciones conteniendo el producto fueron combinadas y concentradas. El residuo se disolvió en 20 mL de acetato de etilo, se lavó con 5 mL de bicarbonato de sodio saturado, se secó sobre $MgSO_4$ y se concentró para proporcionar (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) - 2- (1- pirrolidinilcarbonil) fenil]metil}- 2,5- piperazinadiona (8.8 mg, 16%) como un sólido blanco.

LCMS (B) Rt = 0.77 minutos; m/z $[M+H]^+$ = 566

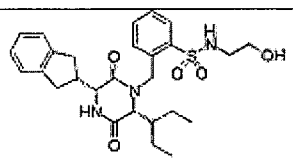
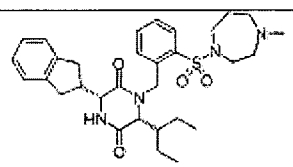
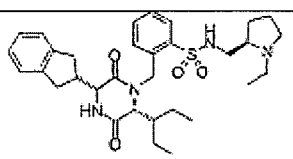
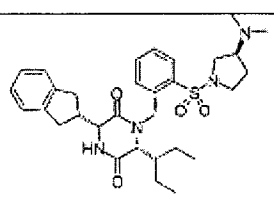
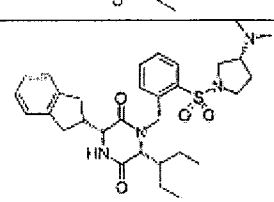
^1H NMR ($CDCl_3$) δ 7.94 (d, 1H) , 7.88 (s, 1H) , 7.54 (d, 1H) , 7.18- 7.26 (m, 4H) , 6.74 (d, 1H) , 5.02 (d, 1H) , 4.42 (d, 1H) , 4.12 (d, 1H) , 4.05 (dd, 1H) , 3.66- 3.70 (m, 2H) , 3.25- 3.31 (m, 1H) , 3.10- 3.23 (m, 4H) , 3.07 (s, 3H) , 2.83- 2.93 (m, 1H) , 2.70- 280 (m, 1H) , 1.90- 2.10 (m, 4H) , 1.450- 1.70 (m, 2H) , 1.20- 1.40 (m, 2H) , 0.97 (t, 3H) , 0.90 (t, 3H) .

Los siguientes ejemplos se prepararon mediante métodos análogos para el ejemplo 208

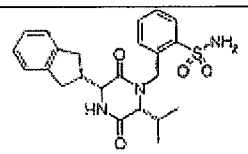
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
209		581.7	0.74 (B)	582	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) - 2- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;
210		594.8	0.64 (B)	595	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- [(4- metil- 1- piperazinil) - carbonil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;
211		583.8	0.76 (B)	584	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- [2- (metiloxi) etil]- 5- (metilsulfonil) benzamida;
211		583.8	0.76 (B)	584	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- (1- metil- 4- piperidinil) benzamida;

212		624.8	0.67 (B)	625	N- [2- (dietilamino) etil]- 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- 5- (metilsulfonil) benzamida;
213		648.9	0.68	649	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- metilsulfonil) - 2- {[(2S) - 2- (1- pirrolidinilmetil) - 1- pirrolidinil]carbonil}fenil) metil]- 2,5- piperazinadiona;

Los siguientes ejemplos se prepararon mediante métodos análogos al ejemplo 89

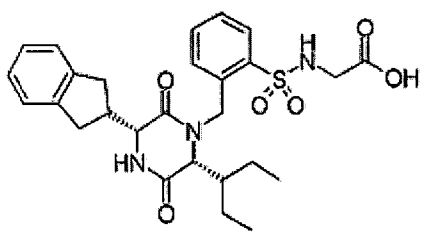
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
214		513.7	3.15	514;	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (2- hidroxietil) bencenosulfonamida;
215		566.8	2.70 (A)	567; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(4- metilhexahidro- 1H- 1,4- diazepin- 1- il) sulfonil]fenil}metil) - 2,5- piperazinadiona;
216		580.8	2.77 (A)	581; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- {[(2R) - 1- etil- 2- pirrolidin]metil}bencenosulfonamida;
217		566.8	2.68 (A)	567; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[(3S) - 3- (dimetilamino) - 1- pirrolidinil]- sulfonil}fenil) metil]- 2,5- piperazinadiona;
218		566.8	2.74 (A)	567; -	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[(3R) - 3- (dimetilamino) - 1- pirrolidinil]- sulfonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

El siguiente ejemplo se preparó mediante un método análogo para el ejemplo 89, iniciando a partir del intermedio 47

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
219		441	3.0 (A)	442; -	2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 2,5- dioxo- 1- piperazinil]- metil}bencenosulfonamida;

Ejemplo 220

N- [(2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) sulfonil]glicina



Se hidrogenó N- [(2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) sulfonil]glicina de fenilmetilo (Int. 16) (60mg) en etanol (3mL) a presión atmosférica en la presencia de paladio sobre carbono (20mol% Pd) y ácido acético (0.5 mL) . El producto resultante se purificó mediante MDAP para proporcionar 3 mg de material puro.

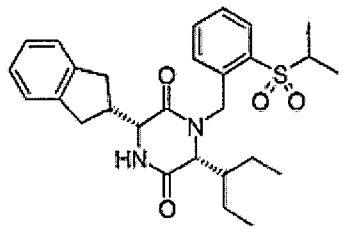
LCMS (A) Rt = 3.28 minutos; m/z $[M+H]^+$ = 528, $[M]^-$ = 526.

^{1}H NMR δ 8.2 (br s, 1H) , 7.97 (d, 1H) , 7.46 (t, 1H) , 7.34 (t, 1H) , 7.10- 7.22 (m, 4H) , 6.97 (d, 1H) , 6.05 (br s, 1H) , 5.58 (br. d, 1H) , 4.88 (br. d, 1H) , 4.31 (d, 1H) , 3.95 (d, 1H) , 3.78 (br.s, 2H) , 2.82- 3.18 (m, 5H) , 1.48- 1.73 (m, 3H) , 1.27 (m, 1H) , 0.86 (m, 6H) .

Ejemplo 221

(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metiletil) - sulfonil]fenil}metil) - 2,5- piperazinadiona

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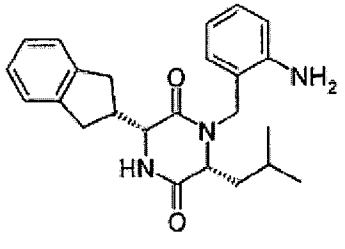
Se agitó (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- mercaptofenil) - metil]- 2,5- piperazinadiona (Int. 19) (100mg) con 2- yodopropano (26uL) y diisopropiletilamina (45uL) en THF (2mL) durante 18 horas luego se agregó tert- butoxido de potasio (29mg) y la mezcla se calentó a 50°C durante 2 horas y se redujo al vacío. El residuo resultante se disolvió en DMC (2mL) y se agregó ácido 3- cloroperoxibenzóico (207 mg) . La mezcla de reacción se agitó durante 48 horas y se pasó a través de una columna SPE de aminopropilo de 2g eluyendo el producto crudo en metanol (10mL) . El eluyente se redujo al vacío y se purificó mediante MDAP para proporcionar 20mg de un sólido blanco.

HPLC (A) Rt = 3.42 minutos; m/z $[M+H]^+$ = 496

^{1}H NMR δ 8.03 (D, 1H) , 7.61 (T, 1H) , 7.48 (t, 1H) , 7.15- 7.35 (m, 5H) , 6.32 (br s, 1H) , 5.32 (d, 1H) , 4.94 (d, 1H) , 4.14 (dd, 1H) , 4.09 (d, 1H) , 3.37 (sex., 1H) , 3.15 (m, 2H) , 2.98 (sept., 1H) , 2.82 (dd, 1H) , 1.63 (m, 2H) , 1.40 (d, 3H) , 1.33 (m, 1H) , 1.29 (d, 3H) , 0.86 (t, 3H) , 0.85 (t, 3H) .

Ejemplo 222

(3R,6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metil- propil) - 2,5- piperazinadiona



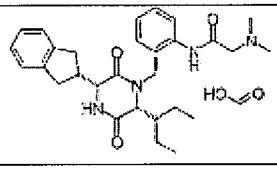
Se agregó por goteo hidrato de hidrazina (0.5g, 10 mmol) a una mezcla de (3R,6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- nitrofenil)

metil]- 2,5- piperazinadiona (ej. 35) y niquel Raney (0.5g) en THF (20mL) . Después de 1 hora el catalizador se filtró y la solución se concentró al vacío para obtener el producto deseado (1.3g, crudo) .

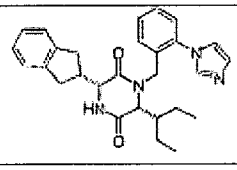
LCMS (D) Rt = 2.63 minutos; m/z $[M+H]^+$ = 392

^{1}H NMR δ 7.27- 7.13 (m, 5H) , 7.05 (d, 1H) , 6.77- 6.67 (m, 3H) , 5.15 (d, 1H) , 4.80 (br s, 2H) , 4.09 (d, 1H) , 4.02 (dd, 1H) , 3.91 (dd, 1H) , 3.20 – 3.06 (m, 3H) , 2.94 – 2.77 (m, 2H) , 1.98 (m, 1H) , 1.78 (m, 1H) , 1.65 (m, 1H) , 1.01 (d, 3H) , 0.95 (d, 3H) .

El siguiente ejemplo se preparó mediante un método análogo para el ejemplo 118

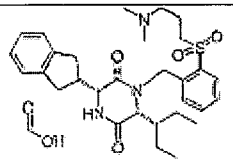
Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
223		490.6	2.56 (A)	491; 489	N`- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - N^2, N^2- dimetilglicinanida

El siguiente ejemplo se preparó mediante un método análogo para el ejemplo 122 excepto que no se utilizó (1R,2R) - (-) - N,N`- dimetilciclohexano- 1,2- diamina.

Ej. No.	Estructura	Peso Mol.	Rt/ min	+ve, - ve	Nombre
224		456	2.72 (A)	457; 455	(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- imidazol- i1) fenil]- metil}- 2,5- piperazinadiona;

El siguiente ejemplo se preparó mediante un método análogo para el intermedio 21, utilizando N,N- dimetil- 3- cloropropilamina como agente alquilante, y la oxidación subsiguiente mediante un método análogo para el intermedio 22 sin aislamiento de azufre intermedio.

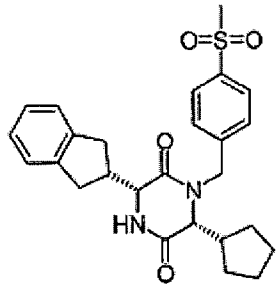
Ej. No.	Estructura	Mwt	Rt/ min	+ve, - ve	Nombre

225		585.7	2.7 (A)	540; 584	ácido formico - (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- dimetilamino) propil]- sulfonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona (1:1)

Ejemplo 226

(3R,6R) - 6- ciclopentil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[4- (metilsulfonil) fenil]-

mrtil}- 2,5- piperazinadiona



Se disolvió bicloruro de {[4- (metilsulfonil) fenil]metil}amina (0.85 g, 3.83 mmol) en metanol(4 mL) y se agregó ciclopentanocarbaldehido (0.31 mL, 3.83 mmol) seguido por ácido (2) - 2,3- dihidro- 1H- inden- 2- il({[(1,1- dimetiletil) oxi]carbonil}- amino) etanóico (1.11 g, 3.83 mmol) y amina de diisopropiletilo (0.63 mL, 3.61 mmol) . La mezcla se agitó durante 15 minutos antes de agregar 4- clorofenilisonitrilo (0.52 g, 3.83 mmol) . La mezcla se agitó durante 2.25 horas y luego se dejo sentar a temperatura ambiente durante la noche (20 horas) antes de ser enfriada en un baño de hielo/agua. Luego se agregó por goteo cloruro de acetilo (1.6 mL, 22.80 mmol) , manteniendo la reacción a temperatura bajo 20°C. Luego la mezcla se agitó en un baño de enfriamiento durante 10 minutos adicionales antes de ser agitada a temperatura ambiente. Después de 18 horas la mezcla se evaporó bajo presión reducida para dejar una goma marrón oscura. La goma se agitó en cloroformo (40 mL) y una solución de bicarbonato de sodio acuoso saturado (40 mL) durante 20 minutos antes de ser diluida con cloroformo (40 mL) y las fases fueron separadas. La fase acuosa se extrajo con cloroformo (3 x 40 mL) . La fase orgánica combinada se secó ($mgSO_4$) y concentró bajo presión reducida. Se agregó cloroformo (40 mL) al residuo y la solución resultante se trató con ácido acético glacial (1.6 mL) y se dejo sentar a temperatura ambiente durante el fin de semana. Luego la mezcla de reacción se lavó con ácido

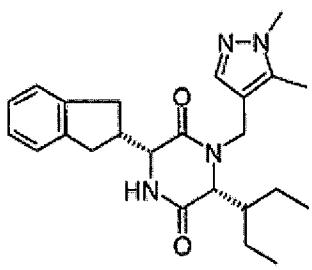
clorhídrico 2M (40 mL) seguido por una solución de bicarbonato de sodio acuoso saturado. La fase orgánica se secó ($MgSO_4$) y se evaporo bajo presión reducida para proporcionar una espuma de color marrón. El residuo se purificó mediante cromatografía rápida sobre gel de sílice [isco, columna RediSep® de 40g, héxanos / EtOAc 10% 60%] para proporcionar 200 mg de (3R,6R) - 6- ciclopentil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[4- (metilsulfonil) fenil]- mrtil}- 2,5- piperazinadiona como un aceite incoloro.

^{1}H NMR $CDCl_3$) δ 7.93 (d, 2H) , 7.77 (d, 1H) , 7.46 (d, 2H) , 7.28- 7.15 (m, 3H) , 5.47 (d, 1H) , 4.14 (m, 2H) , 4.06 (dd, 1H) , 3.75 (d, 1H) , 3.15 (m, 3H) , 3.06 (s, 3H) , 2.87 (m, 2H) , 2.24 (m, 1H) , 2.01 (m, 1H) , 1.80 (m, 2H) , 1.60 (m, 4H) .

HPLC (B) Rt = 0.77 minutos; m/z $[M+H]^+$=467.

Ejemplo 227

(3R,6R) - 3- (2,3- Dihidro- 1H- inden- 2- il) - 1- [(1,5- dimetil- 1H- pirazol- 4- il) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona

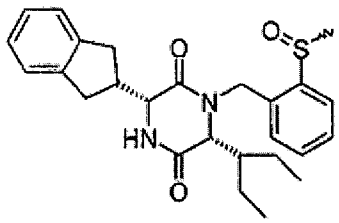


Se aisló hidrocloruro de [(1,5- dimetil- 1H- pirazol- 4- il) metil]amina como la amina libre mediante una columna de intercambio ionico de aminopropilo. A una solución de este material (280 mg) y ácido (2R) - 2,3- dihidro- 1H- inden- 2- il- ({(1,1- dimetiletil) oxi]carbonil}amino) - etanóico (580 mg) en metanol (4 ml) se agregó isocianuro de 2- {[(1,1- dimetiletil) (dimetil) - silil]oxi}fenilo (470 mg) seguido por 2- etilbutanal (250 ul) y tamices moleculares. Luego la reacción se agitó durante la noche. Luego se agregó cloruro de acetilo (1.43 ml) y la reacción se calentó a 50°C durante la noche. La reacción se concentró y el residuo se particionó entre cloroformo y bicarbonato de sodio y se calentó a 50°C durante 6 horas. Luego se agregó trietilamina (3 eq.) y la reacción se agitó a temperatura ambiente durante una semana. La capa orgánica se concentró al vació y el residuo se purificó mediante MDAP.

LCMS (A) Rt = 3.1 minutos; m/z $[M+H]^+$ = 409.

Ejemplos 228- 229

Isómeros de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metil-sulfinil) fenil]metil}- 2,5- piperazinadiona



Se agregó(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]metil}- 2,5- piperazinadiona (ej. 143) (254 mg, 0.58 mmol) a una suspensión agitada de manera vigorosa de alúmina húmeda (580 mg, para preparación ver Synlett, 1992, 235) y ozono (357 mg, 0.58 mmol) en diclorometano (2.9 ml) y la mezcla se calentó cuidadosamente a 40°C y monitoreó mediante LCMS hasta que la reacción se consideró completa. Luego la mezcla de reacción se filtró y concentró para proporcionar un sólido blanco el cual se purificó mediante cromatografía de sílice (SPE, cloroformo, diclorometano, éter, etilacetato, acetona, y metanol) para proporcionar una mezcla 2:1 de epímeros de sulfóxido como un sólido blanco (160 mg) . Una porción de 54 mg de esta mezcla se separó mediante HLPC quiral (Chiralpak AD, eluyente 50% EtOH/heptano, 15 ml/min) para proporcionar:

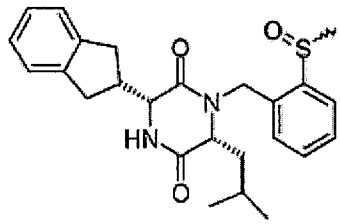
Ejemplo 228, isómero 1 (26 mg) con tiempo de retención HPLC = 11.6 min.
LC/MS (A) Rt = 3.15 minutos; m/z [M+H]+ = 453; m/z [M- formato]$^-$ = 497.

Ejemplo 229, isómero 2 (14 mg) con tiempo de retención HPLC 18.06 min.
LC/MS (A) Rt = 3.17 minutos; m/z [M+H]$^+$ = 453; m/z [M+formato]$^-$ = 497.
La estereoquímica absoluta en azufre para cada uno de estos isómeros actualmente es desconocida.

Ejemplos 230- 231

Isómeros de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2(metil-sulfinil) fenil]etil}- 2,5- piperazinadiona se prepararon a partir del Ejemplo 144 mediante un

método análogo a los Ejemplos 228- 229, utilizando 40% etanol/heptano como eluyente para la separación quiral.



Ejemplo 230, isómero 1

LC/MS (A) Rt = 3.05 minutos; m/z [M+H]+ = 439; m/z [M+formato]$^-$ = 482.

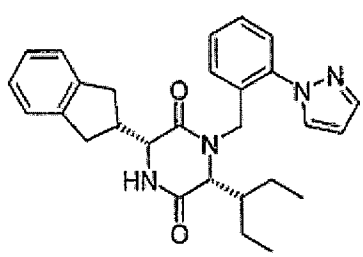
Ejemplo 231, isómero 2

LC/MS (A) Rt = 3.07 minutos; m/z [M+H]$^+$ = 439; m/z [M+formato]$^-$ = 482.

La estereoquímica absoluta en azufre para cada de uno de estos isómeros es actualmente desconocida.

Ejemplo 232

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- pirazol- 1- il) fenil]metil}metil}- 2,5- piperazinadiona



Se agregó secuencialmente carbonato potásico (118 mg) , yoduro cuproso (18mg) , pirazol (58 mg) , 83R,6R) - 1- [(2- bromofenil) metil- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona (ej., 30) (200 mg, 0.4 mmol) y NMP (0.5ml) a un tubo de microondas de 2ml. La mezcla se calentó con agitación a 190°C durante 2 horas en un microondas (Emrys™ Optimizar) . La mezcla de reacción se diluyó con diclorometano y se purificó sobre un cartucho SPE (5g, SCX2) eluyendo con amoniaco/DCM. Las fracciones relevantes fueron evaporadas al vacío a un aceite verde y purificadas adicionalmente sobre un cartucho Si- SPE de 5g eluyendo con metanol en diclorometano (0 a 10%) . La evaporación de la fracción relevante al vacío

proporcionó después de secado por congelamiento a partir de dioxano el compuesto del titulo (100mg) como un sólido de color crema.

LC/MS (A) Rt = 3.41 minutos; m/z $[M+H]^+$ = 457

Ejemplo 233 (3R,6R) - 1- [(2,4- difluorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 5.51 minutos; m/z $[M+H]^+$ = 413; m/z $[M-H]^-$ = 411.

Ejemplo 234 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (metilsulfonil) fenil]metil}- 2,5- piperaziendiona LCMS (A) Rt = 3.01 minutos; m/z $[M+H]^+$ = 455; m/z $[M- H]^-$ = 453.

Ejemplo 235 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(1S) - 1- (4- nitrofenil) etil]- 2,5- piperazinadiona LCMS (A) Rt = 3.43 minutos; m/z $[M+H]^+$ = 436; m/z $[M- H]^-$ = 434.

Ejemplo 236 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [4- nitrofenil) metil]- 2,5- piperazinadiona LCMS (A) Rt = 3.34 minutos; m/z $[M+H]^+$ = 422; m/z $[M- H]^-$ = 420.

Ejemplo 237 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- metil- 5- isoxalozoli) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.01 minutos; m/z $[M+H]^+$ = 3.82; m/z $[M- H]^-$ = 380.

Ejemplo 238 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (4- mofolinil) fenil]metil}- 2,5- piperazinadiona LCMS (A) Rt = 3.31 minutos; m/z $[M+H]^+$ = 462; m/z $[M- H]^-$ = 460.

Ejemplo 239 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1,5- dimetil- 1H- pirazol- 3- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 2.95 minutos; m/z $[M+H]^+$ = 462; m/z $[M- H]^-$ = 460.

Ejemplo 240 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [2- (1- metil- 1H- imidazol- 4- il) etil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 2.33 minutos; m/z $[M+H]^+$ = 395; m/z $[M- H]^-$ = 393.

Ejemplo 241 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1,5- dimetil- 1H- pirazol- 4- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 2.97 minutos m/z $[M+H]^+$ = 395; m/z $[M+formato]^-$ = 439.

Ejemplo 242 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (4- mofolinil) fenil]metil}- 2,5- piperazinadiona LCMS (A) Rt = 3.32 minutos m/z $[M+H]^+$ = 462.

Ejemplo 243 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- oxo- 1,2- dihidro- 3- piridinil) metil]- 2,5- piperazinadiona LCMS (A) Rt = 2.76 minutos; m/z $[M+H]^+$ = 394; m/z $[M- H]^-$ = 392.

Ejemplo 244 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[1- (4- metilfenil) - 1H- pirazol- 4- il]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona ^1H NMR ($CDCl_3$) δ 7.89 (s, 1H) , 7.65 (s, 1H) , 7.52 (d, 2H) , 7.26- 7.13 (m, 5H) , 6.93 (d, 1H) , 5.08 (d, 1H) , 4.02- 3.90 (m, 3H) , 3.10 (m, 3H) , 2.95- 2.75 (m, 2H) , 2.38 (s, 3H) , 2.0 (m, 1H) , 1.90- 1.60 (m, 3H) ,1.02 (d, 3H) ,0.97 (d, 3H) .

Ejemplo 245 N- (3- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperzinil]metil}fenil) - N- metilacetamida ^1H NMR ($CDCl_3$) δ 7.50 (d, 1H) , 7.39 (t, 1H) , 7.25- 7.07 (m, 6H) , 5.32 (d, 1H) , 4.06 (dd, 1H) , 3.97 (d, 1H) , 3.47 (s, 1H) , 3.24 (s, 3H) , 3.17- 3.07 (m, 3H) , 2.95- 2.75 (m, 2H) , 2.0- 1.75 (m, 5H) , 1.68- 1.57 (m, 1H) ,0.95 (d, 3H) , 0.93 (d, 3H) .

Ejemplo 246 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[5- (2- piridinil) - 2- tienil]metil}- 2,5- piperazinadiona LCMS (A) Rt = 3.36 minutos; m/z $[M+H]^+$ = 460; m/z [M- formato]$^-$ = 504.

Ejemplo 247 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(1 S) - 1- (4- metil- 1,3- tiazol- 2- il) etil] - 2,5- piperazinadiona LCMS (A) Rt = 3.21 minutos; m/z $[M+H]^+$ = 412; m/z [M+formato]$^-$ = 456.

Ejemplo 248 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(5- metil- 3- fenil- 4- isoxazolil) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.34 minutos; m/z $[M+H]^+$ = 458; m/z $[M- H]^-$ = 502.

Ejemplo 249 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1,3- dimetil- 1H- pirazol- 4- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 2.91 minutos; m/z $[M+H]^+$ = 395.

Ejemplo 250 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (1H- pirazol- 1- il) fenil]metil- 2,5- piperazinadiona LCMS (B) Rt = 0.83 minutos; m/z $[M+H]^+$ = 443.

Ejemplo 251 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- (3- isoxazolilmetil) - 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.00 minutos; m/z $[M+H]^+$ = 368; m/z $[M-H]^-$ = 366.

Ejemplo 252 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(5- metil- 2- pirazinil) metil]- 2,5- piperazinadiona LCMS (A) Rt = 2.93 minutos; m/z $[M+H]^+$ = 393.

Ejemplo 253 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1- metil- 1H- bezimidazol- 2- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 2.96 minutos; m/z $[M+H]^+$ = 431; m/z $[M- H]^-$ = 429.

Ejemplo 254 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [3- {[(1,1- dimetiletil) oxi]metil}fenil) metil}- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.61 minutos; m/z $[M+H]^+$ = 463.

Ejemplo 255 (3R,6R) - 1- [(4- acetilfenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.30 minutos; m/z $[M+H]^+$ = 419; m/z $[M-H]^-$ = 417.

Ejemplo 256 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- fenil- 2H- 1,2,3- triazol- 4- il) metil]- 2,5- piperazinadiona LCMS (A) Rt = 3.53 minutos; m/z $[M+H]^+$ = 444.

Ejemplo 257 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- (fenilmetil) - 2,5- piperazinadiona LCMS (A) Rt = 3.36 minutos; m/z $[M+H]^+$ = 377; m/z [M+formato]$^-$ = 421.

Ejemplo 258 (3R,6R) - 1- [(4- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.52 minutos; m/z $[M+H]^+$ = 411.

Ejemplo 259 3- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida LCMS (A) Rt = 2.96 minutos; m/z $[M+H]^+$ = 434; m/z $[M- H]^-$ = 432.

Ejemplo 260 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[3- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona LCMS (A) Rt = 3.03 minutos; m/z $[M+H]^+$ = 455; m/z $[M- H]^-$ = 453.

Ejemplo 261 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N,N- dimetilbencenosulfonamuro LCMS (A) Rt = 3.21 minutos; m/z $[M+H]^+$ = 484; m/z $[M- H]^-$ = 482.

Ejemplo 262 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona LCMS (B) Rt = 0.74 minutos; m/z $[M+H]^+$ = 490.

Ejemplo 263 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- metil- 1,2,4- oxadiazol- 5- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.01 minutos; m/z $[M+H]^+$ = 383; m/z $[M- H]^-$ = 381.

Ejemplo 264 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- ({[4- [trifluorometil) sulfonil]fenil}metil) - 2,5- piperazinadiona LCMS (A) Rt = 3.49 minutos; m/z $[M+H]^+$ = 509.

Ejemplo 265 (3R,6R) - 1- {[2- cloro- 4- (metilsulfonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.15 minutos; m/z $[M+H]^+$ = 489/491; m/z $[M- H]^-$ = 487/489.

Ejemplo 266 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(5- metil- 1- fenil- 1H- pirazol- 4- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 3.21 minutos; m/z $[M+H]^+$ = 457; m/z [Mçformato]$^-$ = 501.

Ejemplo 267 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(4- {[etil(metil) amino]metil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona LCMS (A) Rt = 2.59 minutos; m/z $[M+H]^+$ = 462; m/z [M+formato]$^-$ = 506.

Ejemplo 268 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1- pirrolidinilmetil) fenil]metil}- 2,5- piperazinadiona LCMS (A) Rt = 2.61 minutos; m/z $[M+H]^+$ = 474.

Ejemplo 269 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- metilsulfonil) fenil]metil}- 6- fenil- 2,5- piperazinadiona ^1H NMR ($CDCl_3$) δ 8.08 (d, 1H) , 7.60 (m, 2H) , 7.49 (t, 2H) , 7.33 (d, 1H) , 7.25- 7.15 (m, 4H) , 5.48 (d, 1H) , 4.71 (d, 1H) , 4.07 (dd, 1H) , 3.87 (d, 1H) , 3.25 (s, 3H) , 3.19 (dd, 1H) , 3.12 (m, 2H) ,2.98- 2.81 (m, 2H) .

Ejemplo 270 (3R,6R) - 6- clclohexil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona LCMS (A) Rt = 3.65 minutos; m/z $[M+H]^+$ = 417; m/z [M+formato]$^-$ = 461.

Ejemplo 271 (3R,6R) - 6- ciclopropil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona LCMS (A) Rt = 3.24 minutos; m/z $[M+H]^+$ = 375; m/z [M+formato]$^-$ = 419.

Ejemplo 272 hidrocloruro de (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 1- {[2- 1- piperazinilsulfonil) fenil]metil}- 2,5- piperazinadiona LCMS (A) Rt = 3.79 minutos; m/z $[M+H]^+$ = 491; m/z $[M- H]^-$ = 489.

Ejemplo 273 3- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoato de 1,1- dimetiletil LCMS (A) Rt = 3.77 minutos; m/z $[M+H]^+$ = 491; m/z $[M- H]^-$ = 489.

Ejemplo 274 (3S,6S) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona LCMS (A) Rt = 3.25 minutos; m/z $[M+H]^+$ = 469; m/z $[M- H]^-$ = 467.

Ejemplo 275 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (2- pirazinilamino) fenil]metil}- 2,5- piperazinadiona LCMS (B) Rt = 0.78 minutos; m/z $[M+H]^+$ = 470.

Ejemplo 276 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (1H- 1,2,3- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona LCMS (B) Rt = 0.76 minutos; m/z $[M+H]^+$ = 444.

Ejemplo 277 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (1H- 1,2,4- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona LCMS (B) Rt = 0.75 minutos; m/z $[M+H]^+$ = 444.

Ejemplo 278 (3R,6R) - 6- ciclopentil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[4- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona LCMS (B) Rt = 0.76 minutos; m/z $[M+H]^+$ = 502.

Ejemplo 279 N- (2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - 4- morfolinecarboxamuro HPLC (D) Rt = 2.92 minutos; m/z $[M+H]^+$ = 519.

Ejemplo 280 (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (2H- 1,2,3- triazol- 2- il) fenil]metil}- 2,5- piperazinadiona LCMS (B) Rt = 0.85 minutos; m/z $[M+H]^+$ = 444.

Ejemplo 281 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) benzamida LCMS (B) Rt = 0.69 minutos; m/z $[M+H]^+$ = 464.

Ejemplo 282 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2.5- dioxo- 1- piperazinil]metil}- N- metil- N- [2- (metiloxi) etil]benzamida LCMS (D) Rt = 2.62 minutos; m/z $[M+H]^+$ = 492.

Ejemplo 283 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) - N- metilbenzamida LCMS (D) Rt = 2.39 minutos; m/z $[M+H]^+$ = 478.

Ejemplo 284 N- (2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - 4- morfolinecarboxamuro LCMS (B) Rt = 0.76 minutos; m/z $[M+H]^+$ = 505.

Ejemplo 285 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (dimetilamino) etil]- N- metilbenzamida LCMS (D) Rt = 2.29 minutos; m/z $[M+H]^+$ = 505.

Ejemplo 286: La preparación de este compuesto se ha descrito como Intermdedio 14: (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (hidroximetil) fenil]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona.

Ejemplo 287: La preparación de esté compuesto se ha descrito como Intermedio 15: 3- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoato de 1,1- dimetiletil.

Ejemplo 288: La preparación de esté compuesto se ha descrito como Intermedio 45: (3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(1,1- dimetiletil) tio]fenil}metil) - 6- (1- metiletil) - 2,5- piperazinadiona.

Ejemplo 289: La preparación de esté compuesto se ha descrito como Intermedio 52: Ácido 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- 1,3- bencenodicarboxílico.

Ejemplo 290: La preparación de esté compuesto se ha descrito como Intermedio 53: Ácido 2- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- (metilsulfonil) benzóico.

Ejemplo 291: La preparación de esté compuesto se ha descrito como Intermedio 54: 4- {[(3R,6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoato de 1,1- dimetiletil.

Procedimientos de Ensayo

Ensayo 1) Determinación de afinidad antagonista en receptores de oxitoxina- 1 humano utilizando FLIPR

Cultivo Celular

Células adherentes de Ovario de Hamster Chino, expresando de manera estable el receptor de Oxitocina humano (hOT) recombinante, se mantuvieron en cultivo en medio DMEM:F12 (Sigma, número de catalogo D6421) , suplementadas con suero de ternero fetal inactivado por calor al 10% (Gibo/Invitrogen, número de catalogo 01000- 147) , 2mM L- glutamina (Gibco/Invitrogen, número de catalogo 25030- 024) y 0.2mg/ml G418 (Gibco/Invitrogen, número de catalogo 10131- 027) . Las células se cultivaron como monocapas bajo 95%:5% aire:CO2 a 37°C y se sometieron a pasaje (subcultivo) cada 3- 4 días utilizando TrypLE™ Express (Gibco/Invitrogen, número de catalogo 12604- 013) .

Medición de [Ca2+]i utilizando el FLIPR™

Se sembraron células CHO- hOT en placas de 384 pozos de base transparante y pared negra (Nunc) a una densidad de 10.000 células por pozo en medio de cultivo como se describió anteriormente y se mantuvieron durante la noche (95%:5% aire:CO2 a 37°C) . Después de retirar el medio de cultivo, las células se incubaron durante 1h a 37°C en Medio de Tyrode (NaCl, 145mM; KCl, 2.5mM; HEPES, 10mM; Glucosa, 10mM; MgCl2, 1.2mM; $CaCl_2$,1.5mM) conteniendo probenacid (0.7 mg/ml) , el indicador de calcio citoplásmico, Fluo- 4 (4uM; Teflabs, USA) y el agente enfriador Brilliant Black (250uM; Molecular Devices, UK) . Luego las células se incubaron durante 30 min adicionales a 37°C con ya sea amortiguador solo o amortiguador conteniendo antagonista OT, antes de ser colocado en un FLIPR™ (Molecular Devices, UK) para monitorear la fluorescencia molecular (λ_{ex} = 488nm, λ_{EM} = 540nm) antes y después de la adición de una concentración submáxima de oxitocina (EC80) .

Análisis de Datos

Respuestas funcionales utilizando FLIPR se analizaron utilizando Activity Base Version 5.0.10.

Ensayo 2) Determinación de afinidad antagonista estimada en receptores de Oxitoxina- 1 humano utilizando Polarización de Fluorescencia

Cultivo Celular

Células adherentes de Ovario de Hamster Chino (CHO) , expresando de manera estable el receptor de Oxitoxina- 1 humano recombinante, se mantuvieron en cultivo en medio DMEM:F12 (Sigma, número de catálogo D6421) , suplementadas con suero de ternero fetal al 10% (Gibco/Invitrogen, número de catalogo 01000- 147) , 2mM L- glutamina(gibco/invitrogen, número de catalogo 25030- 024) y 0.5mg/ml G418 (Gibco/Invitrogen, número de catalogo 10131- 027) . Las células se cultivaron como monocapas bajo 95%:5% aire:Co2 a 37°C y se pasaron cada 3- 4 días utilizando HBSS + 0.6mM EDTA.

Preparación de Membranas (Expresión Genética y Bioquímica proteica de GSK Reino Unido)

Las membranas se prepararon a partir de células cultivadas en botellas giratorias de 1800 cm2. Las células cosechadas (HBSS + 0.6 mM EDTA) se centrifugaron a 250 g durante 5 min a 4°C. Esto se repitió después de re- suspender las pellets en 200 mls sobre HBSS + 0.6 mM EDTA. Todos los pasos subsiguientes se realizaron a 4°C. Las células se homogenizaron durante 2 x 15 secs en 200 mls de 50 mM HEPES + 10- 4M leupeptinaa + 25ug/ml bacitracina + 1mM EDTA + 1mM PMSF + 2uM Pepstatina A, (los últimos dos reactivos se agregaron como concentraciones frescas x100 y x500 respectivamente en etanol) . El homogenato se precipitó sobre hielo durante 5 min después del primer rompimiento y 10- 40 minutos después del rompimiento final para disipar la espuma. Luego el homogenato se centrifugó a 500g durante 20 mins y el sobrenadante se centrifugó durante 36 mins a 48.000g. El pellet se re- suspendió en el mismo amortiguador como antes pero sin PMSF y Pepstatina A. Luego el material se forzó a través de una aguja de 0.6 mm, llevado al volumen requerido, (usualmente x4 el volumen del pellet celular original) , dividido en alícuotas y almacenado congelado a - 80°C.

Medición de Unión OT utilizando Polarización de Fluorescencia

Se prepararon los compuestos como diluciones seriales 1 en 4 en DMSO al 100%. El compuesto diluido se agregó a microplacas black Greiner 384 a 0.5ul/pozo. La oxitocina rotulada Bodipy

Tamra (Parking Elmer Life Sciences pepido de cliente CUS54801) se diluyó en amortiguador de ensayo (10mM HEPES, 10mM MgCl2, 0.125 mg/ml de albumina de suero humano: pH7.4 con KOH) y se agregó a la microplaca para proporcionar una concentración de ensayo final de 0.5 nM @ 20ul/pozo, seguido por adición de membrana CHO- hOT, diluida en amortiguador de ensayo, 20ul/pozo, para proporcionar una concentración de ensayo final de 2.5ug/pozo. Las placas se protegieron de la luz y se incubaron a temperatura ambiente durante 2 horas antes de ser leídas sobre un Analyst LJL (de Molecular Devices) utilizando longitud de onda de filtro de excitación 535/22, filtro de emisión: longitud de onda 580/30.

Análisis de Datos

Las unidades de polarización de fluorescencia tanto de lecturas paralelas como perpendiculares se utilizaron para calcular la Anisotropia & Intensidad Total de los compuestos. Los valores de anistropía fueron sometidos a conversión de normalización y luego acoplados a la ecuación logística de 4 parámetros. Como el ensayo está proporcionando un estimado de afinidad de receptor, se aplicó corrección pKi funcional (relación Cheng Prusoff) , asumiendo el pKd de Bodipy Tamra como 9.9 (se añadió una concentración de ligandos 4x) . Todos los análisis se realizaron utilizando Activity Base version 5.0 (IDBS) .

Actividad y utilidad de los compuestos del invento

Se encontró que los ejemplos 1- 185 y 187- 232 tuvieron al menos uno de:

i) un valor pKi de 6.9 o más en Ensayo 1;

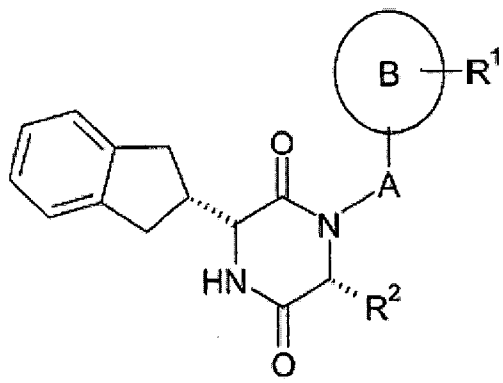
ii) un valor pKi de 7.5 o más en Ensayo 2.

Se encontró que los ejemplos 233- 285 tuvieron actividad medible en al menos uno entre el Ensayo 1 y Ensayo 2. Los ejemplos 233- 285 también pueden tener utilidad como Intermedios en la preparación de otros compuestos de la Formula (I) o Formula (A) .

Los Ejemplos 186 y 286- 291 no fueron probados en los Ensayos y tienen utilidad como Intermedios en la preparación de otros compuestos de la Formula (I) o Formula (A) .

Reivindicaciones

1. Una o más entidades químicas seleccionadas a partir de un compuesto de la Formula (I)



(I)

y derivados fisiológicamente aceptables del mismo,

en donde:

A representa un grupo C1- 4alquileno opcionalmente sustituido por uno o más grupos C1- 4alquilo;

El anillo B representa un grupo arilo o heteroarilo mono- , bi- o tricíclico que contiene uno o más heteroátomos independientemente seleccionados de O, S o N, en donde el grupo arilo o heteroarilo se puede opcionalmente sustituir por uno o más grupos R^1 los cuales se pueden seleccionar independientemente de C1- 6cicloalquilo, C1- 6alquilo, C1- 6cicloalcoxilo, C1- 6alcoxilo, arilo, aralquilo, heterocicliclo, heteroarilo, - Oheterociclilo, - Oheteroarilo, - S(O) nheterociclilo o –S(O) nheteroarilo (cada uno de los cuales se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4) ; o R1 se puede seleccionar independientemente de halo, hidroxilo, - NR3R4,

nitro, ciano, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, carboxilo, - CONR3R4, - COR5, - S(O) nR6, - NR7COR8, - S(O) mNR9R10 o –NR11S(O) mR12;

R^2 representa C3- 7alquilo, C3- 7cicloalquilo o fenilo, cada uno de los cuales se puede sustituir opcionalmente por uno o más grupos seleccionados de C1- 4alquilo o C3- 7cicloalquilo;

R^3 y R^4 independientemente representan H, C1- &alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir por uno o mas grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, C1- 3alcoxiC1- 6alquilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, COR^5, heteroarilo, heterociclilo, arilo o $–NR^3aR^4a$;

O R^3 y R^4, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un heteroarilo de 5 o 6 miembros o un anillo heterociclilo de 4 a 7 miembros, tal anillo pueden adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - $NR^{3a}R^{4a}$, COR^5, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alkoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, COR^5, heteroarilo, heterociclilo, arilo o $–NR^{3a}R^{4a}$) ;

R3a y R4a independientemente representan H, C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, o arilo.

O R^{3a} y R^{4a}, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un heteroarilo de 5 o 6 miembros o un anillo heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alcoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente solucionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, o arilo) ;

R^5 representa C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 6alquilo, arilo, heteroarilo o heterociclilo, en donde los grupos C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 6alquilo, arilo, heteroarilo o heterociclilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4;

R^6 representa C1- 6alquilo, C1- 6cicloalquilo, trifluoroC1- 6alquilo, arilo, heteroarilo, o heterociclilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, trifluoroC1- 6alquilo, arilo, heteroarilo, o heterociclilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, c1- 6alquilo, C1- 6- alcoxilo, C1- 3alcoxiloC1- 6alquilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, heteroarilo, heterociclilo, arilo o $–NR^3R^4$;

R7 representa H o C1- 4alquilo (opcionalmente sustituido por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

R8 representa C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo cada uno de los cuales se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

O R7 y R8 junto con los átomos de interconexión a los cuales está unidos forman un anillo de heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener uno o más heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo se puede opcionalmente sustituir por uno o más grupos seleccionados seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o –NR^3R^4;

R9 y R10 independientemente representan H, C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo en donde los grupos C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo o heteroarilo se pueden opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, arilo, NR^3R^4 o heterociclilo opcionalmente sustituido por C1- 6alquilo;

O R^9 y R^{10}, junto con el átomo de interconexión al cual están unidos forman un anillo heteroarilo de 5 o 6 miembros o heterociclico de 4 a 7 miembros, tal anillo adicionalmente puede contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heteroarilo de 5 o 6 miembros o heterociclilo de 4 a 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, C1- 4alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, - $NR^{3a}R^{4a}$, COR^5, hidroxilo, arilo, heteroarilo o heterociclilo (en donde los grupos C1- 4alquilo, C1- 4alkoxilo, arilo, heteroarilo o heterociclilo sobre el anillo de heteroarilo de 5- a 6 miembros o heterociclilo de 4- a 7 miembros se pueden opcionalmente sustituir además por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o –$NR^{3a}R^{4a}$) ;

R^{11} representa H o C1- 4alquilo (opcionalmente sustituido por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

R^{12} representa C1- 6alquilo C1- 6alquilo, C1- 6cicloalquilo, arilo, heterociclilo, o heteroarilo cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, c1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo. –S(O) nR6, heteroarilo, heterociclilo, arilo o NR^3R^4) ;

O R11 y R12 junto con los átomos de interconexión a los cuales están unidos forman un anillo heterociclilo de 4 a 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alkoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alkoxilo, - S(O) nR^6, heteroarilo, heterociclilo, arilo o $–NR^3R^4$;) ;

n representa 0, 1 o 2;

y m representa 1 o 2.

2. Al menos una entidad química que comprende un compuesto de la Formula (IA) y derivados fisiológicamente aceptables, en donde el compuesto de la Formula (IA) es un compuesto de la Formula (I) como se definió en la reivindicación 1 el cual es diferente de

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (2- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (4- nitrofenil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (4- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- (4- piridinilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (5,6,7,8- tetrahidroimidazo[1,5- a]piridin- 1- il) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[6- (trifluorometil) - 3- piridinil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [2- (1- metil- 1H- imidazol- 2- il) etil1- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (3- piridinil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [2- (1- metil- 1H- imidazol- 5- il) etil]- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (2- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {2- [4- (metilsulfonil) fenil]- etil}- 2,5- piperazinadiona;

N- (3- {2- [(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazina]etil}fenil) metanosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(1- metil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- metil- 2H- tetrazol- 5- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1- etil- 5- metil- 1H- pirazol- 4- il) - metil]- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(1- etil- 1H- pirazol- 4- il) metil]- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[1- metil- 5- (trifluorometil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona;

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(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- metilamino) metil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[3,5- bis(trifluorometil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 6- ciclopropil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]- metil- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3- metilfenil) metil]- 6- fenil- 2,5- piperazinadiona; y (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2- (2- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- dimetilamino) propil]sulfonil}fenil) - metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

3. Al menos una entidad química según la reivindicación 1 o reivindicación 2 en donde A representa CH_2, $CH(CH_3)$ o CH_2CH_2.

4. Al menos una entidad química según cualquier reivindicación anterior en donde el anillo B representa fenilo, piridilo, pirimidinilo, quinolinilo o pirazolilo.

5. El menos una entidad química según cualquier reivindicación anterior en donde uno o más grupos R1 se puede independientemente seleccionar de C1- 6alquilo, C1- 6alcoxilo, arilo, aralquilo, heterociclilo, heteroarilo, (cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de hidroxilo, C1- 6alquilo, C1- 6alcoxilo, heterociclilo, arilo o –NR3R4) ; o R1 se puede adicionalmente independientemente seleccionar de halo, hidroxilo, - NR3R4, nitro, ciano, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, carboxilo, - CONR3R4, - COR5, - S(O) nR6, - NR7COR8, - S(O) mNR9R10 o –NR11S(O) mR12;

6. Al menos una entidad química según cualquier reivindicación anterior en donde R2 representa C3- 5alquilo, o R2 representa C3- 5cicloalquilo el cual se puede además opcionalmente sustituir por C1- 2alquilo, en donde el número total de átomos de carbono en el grupo R2 está entre 3 y 5.

7. Al menos una entidad química según cualquier reivindicación anterior en donde R3 y R4 independientemente representan H o C1- 4alquilo el cual opcionalmente es sustituido por uno o más grupos independientemente seleccionados de hidroxilo, C1- 2alquilo o –NR3aR4a, o R3 y R4, junto con el átomo de nitrógeno de interconexión al cual están unidos forman un anillo heterociclilo de 5 o 6 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo de 5 o 6 miembros puede opcionalmente además ser sustituido por C1- 4alquilo.

8. Al menos una entidad química según cualquier reivindicación anterior en donde R3a y R4a independientemente representan C1- 6alquilo.

9. Al menos una entidad química según cualquier reivindicación anterior en donde R5 representa C1- 6alcoxilo el cual opcionalmente es sustituido con hidrófilo, C1- 6alcoxilo, o –NR3R4.

10. Al menos una entidad química según cualquier reivindicación anterior en donde R6 representa C1- 6alquilo, trifluoroC1- 6alquilo o heterociclilo, cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de C1- 6alquilo, C1- 3alcoxiC1- 6alquilo, heterociclilo o –NR3R4.

11. Al menos una entidad química según cualquier reivindicación anterior en donde R7 representa H o C1- 4alquilo.

12. Al menos una entidad química según cualquier reivindicación anterior en donde R8 representa C1- 6alquilo o heterociclilo cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de C1- 6alquilo, o –NR3R4.

13. Al menos una entidad química según cualquier reivindicación anterior en donde R9 y R10 independientemente representan H, C1- 6alquilo, heterociclilo o heteroarilo cada uno de estos se puede opcionalmente sustituir por uno o más grupos independientemente seleccionados de hidroxilo, carboxilo, C1- 6alquilo, arilo, - NR3R4 o heterociclilo opcionalmente sustituidos por C1- 6alquilo, o R9 y R10, junto con el átomo de nitrógeno de interconexión al cual están unidos

forman un anillo heterociclilo de 5, 6 o 7 miembros, tal anillo puede adicionalmente contener 1 o 2 heteroátomos independientemente seleccionados de O, S o N; y en donde el anillo heterociclilo de 5, 6 o 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de O, S o N; y en donde el anillo heterociclilo de 5 , 6 o 7 miembros se puede opcionalmente sustituir por uno o más grupos seleccionados de C1- 4alquilo, o –NR3R4, (en donde el grupo c1- 4alquilo se puede además opcionalmente sustituir por C1- 6alcoxilo) .

14. Al menos una entidad química según cualquier reivindicación anterior en donde R11 representa H o C1- 4alquilo.

15. Al menos una entidad química según cualquier reivindicación anterior en donde R12 representa C1- 6alquilo.

16. Al menos una entidad química según cualquier reivindicación anterior en donde R11 y R12 junto con los átomos de interconexión a los cuales están unidos forman un anillo heterociclilo de 5 o 6 miembros, tal anillo puede adicionalmente contener uno o más heteroátomos independientemente seleccionados de O, S o N, y en donde el anillo heterociclilo se puede además opcionalmente sustituir por uno o más grupos independientemente seleccionados de halo, hidroxilo, carboxilo, C1- 6alquilo, C1- 6alcoxilo, trifluoroC1- 4alquilo, trifluoroC1- 4alcoxilo, -S(O) nR6, heteroarilo, heterociclilo, arilo o –NR3R4.

17. Al menos una entidad química según cualquier reivindicación anterior en donde n representa 2.

18. Al menos cualquier entidad química según cualquier reivindicación anterior en donde m representa 2.

19. Al menos una entidad química según cualquier reivindicación anterior seleccionada del grupo que consta de:
(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 1- [2- (hidroximetil) bencil]- piperazina- 2,5- diona;

metil 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (metiloxi) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metiloxi) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiloxi) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (trifluorimetil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 1- [(3- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- fluorofenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 1- (2- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 1- {[3- (1- piperidinilmetil) - fenil]metil}- 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[2- (dimetilamino) etil]oxi}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- fluorofenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(3- fluorofenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- fluorometil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluorometil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- fluorometil) oxi]- fenil}- metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({3- [trifluorometil) oxi]- fenil}- metil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,6- bis(metiloxi) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,6- diclorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- piridinilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2,2- dimetilpropil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1R) - 1- feniletil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2,6- dimetil- 3- piridinil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,4- bis(metiloxi) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(2- bromofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetil- bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- hidroxifenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(3- nitrofenil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(2- nitrofenil) metil- 2,5- piperazinadiona;

(3R, 6R) - 1- ({3- difluorometil) oxi]fenil}metil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (1,2,3- tiadiazol- 4- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 1- [3- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(3,4- diclorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- etilpropil) - 1- {[2- (4- morfolin) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- {[3,5- bis(metiloxi) fenil]- metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(trifluorometil) oxi]- fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(3,5- dimetilfenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (fenilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(4- clorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[3- (2- piridiniloxi) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 6- ciclohexil- 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilfenil) - 1- {[2- (metilsulfonil) fenil]- metil}-

2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 1- {[2- (metilsulfonil) fenil]- metil}-

2,5- piperazinadiona;

(3R, 6R) - 6- (diciclopropilmetil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2,2- dimetilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(trifluorometil) - sulfonil]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metiloxi) - 4- (metilsulfonil) fenil]- metil}- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiloxi) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- {[2- cloro- 4- (metilsulfonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(5- metil- 1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- (1,1- dimetil) tio]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- metil- 5- (trifluorometil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (metilsulfonil) - 2- piridinil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (2- nitrobencil) piperazina- 2,5- diona;

ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil}benzoico;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil}benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- (1- metil- 4- piperidinil) benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2{[4- (dimetilamino) - 1- piperidinil]- carbonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (1- metil- 4- piperidinil) benzamida formato;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (dimetilamino) etil]- N- metilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [3- (dimetilamino) propil]- N- metilbenzamida formato;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [3- (dimetilamino) propil]- N- metilbenzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (dimetilamino) etil]benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(4- metil- 1- piperazinil) - carbonil]fenil}metil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (4- morfolinil) etil]benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (2- hidroxietil) benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (2- hidroxietil) - N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- 4- piperidinilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperazinilcarbonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- dimetilamino) metil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbencenosulfonamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetil- bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- morfolinilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benceno- sulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- metil- 1- piperazinil) - sulfonil]fenil}- metil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (1- metil- 4- piperidinil) - bencenosulfonamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etil- propil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- (1- metil- 4- piperidinil) - bencenosulfonamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (4- morfolin) etil]benceno- sulfonamida;

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2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- [2- (dimetilamino) etil]bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(4- etil- 1- piperazinil) sulfonil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- ({4- [2- (metiloxi) etil]- 1- piperazinil}sulfonil) fenil]metil}- 2,5- piperazinadiona;

hidrocloruro de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperazinilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1- piperidiniltio) - fenil]metil}- 2,5- piperazinadiona;

hidrocloruro de (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (4- piperazinilsulfonil) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- ({1- [2- (metiloxi) - etil]- 4- piperidinil}sulfonil) metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- {[3- (4- morfolinil) propil]- tio}fenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- {[3- (4- morfolin) propil]- sulfonil}fenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- (dimetilamino) propil]tio}fenil) metil]—6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metil- 4- piperidinil) - tio]fenil}metil) - 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metil- 4- piperidinil) - sulfonil]fenil}metil) - 2,5- piperazinadiona formato;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({2- [(1- etil- 4- piperidinil) - sulfonil]fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(2- aminofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona formato;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) metanosulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) etano- sulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - 2- propanosulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - N- metilmetanosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (1,1- dioxido- 2- isotiazolidinil) fenil]metil}- 6- (1- etilpropil) - 2,5- piperazinadiona;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) acetamida;

N^1- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - N^3, N^3- dimetil- β- alaninamida formato;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - 4- (dimetil- amino) butanamida formato;

(ácido formico - N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}fenil) - 1- metil- 4- piperadinacarboxamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (2- oxo- 1- pirrolidin) - fenil]metil}- 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil- 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbencenosulfonamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil- 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[etil(metil) amino]metil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [(1- fenil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[1- (3metilfenil) - 1H- pirazolo- 4- il]metil}- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- [2(3- piridinil) etil]- 2,5- piperazinadiona;

N- (3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- .metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) metanosulfonamida;

N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - N- metilacetamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {2- [4- (metiloxi) - 3- (metilsulfonamida) fenil]- etil}- 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1- metil- 1H- pirazol- 4- il) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(1S) - 1- feniletil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (3- piridinilmetil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- (4- piridinilmetil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1,1- dimetilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- oxo- 1,2- dihidro- 3- piridinil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(2- hidroxifenil) metil]- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[1- (fenilmetil) - 1H- pirazol- 4- il]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- [(2,4- diclorofenil) metil]- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- (2- bifenililmetil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [2- (3- piridinil) etil]- 2,5- piperazinadiona;

(3R, 6R) - 1- {[3,4- bis(metiloxi) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metiltio) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(4- {[2- (dimetilamino) etil]oxi}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (1- pirrolidinilmetil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinilmetil) - fenil]metil}- 2,5- piperazinadiona;

ácido formico - (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({3- [(dimetilamino) metil]- fenil}metil) - 6- (1- etilpropil) - 2,5- piperazinadiona (1:1) ;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 1- [(3- metilfenil) metil]- 2,5- piperazinadiona;

N- ciclopropil- 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metilpropil) - 1- {[3- (3- piridinil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluoro- 2- (hidroximetil) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (2- pirazinilamino) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (2- pirimidinilamino) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[4- (2- pirimidinilamino) - fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(1- metil- 1H- imidazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- [(1- metil- 1H- imidazol- 2- il) amino]fenil}metil) - 6- (2- metilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(5- metil- 1,3,4- tiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- ({4- [(5- metil- 1,3,4- tiadiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({4- [(5- metil- 1,3,- tiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- ({4- [(5- metil- 1,3,- tiazol- 2- il) amino]fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {4[- (1H- pirazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1H- 1,2,3- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (1H- 1,2,4- triazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (2H- 1,2,3- triazol- 2- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (1H- tetrazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- tetrazol- 1- il) fenil]metil}- 2,5- piperazinadiona;

ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluorobenzóico;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluoro- N,N- dimetilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- fluoro- 2- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- 5- fluoro- N- (2- hidroxietil) benzamida;

ácido 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]benzoico;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}benzamida;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N- dimetilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metilbenzamida;

ácido 3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico;

3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

3- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[3- (4- morfolinilcarbonil) fenil]metil}2,5- piperazinadiona;

ácido 4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzoico;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}benzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) benzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- metil- N- [2- (metiloxi) etil]benzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- [2- (dimetilamino) etil]- N- metilbenzamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]metil}- N- (2- hidroxietil) - N- metilbenzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- ({4- [(4- metil- 1- piperazinil) carbonil]- fenil}metil) - 6- (2- metilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- {1- [2- (metiloxi) etil]- 4- piperadinil}benzamida;

(3R, 6R) - 1- {[2,4- bis(hidroximetil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metiltio) - fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,4- bis(1- pirrolidincarbonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 1- {[2,4- bis(4- morfolinilcarbonil) fenil]metil}- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N,N`,N`- tetrametil- 1,3- bencenodicarboxamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- bis(2- hidroxietil) - N,N´- dimetil- 1,3- bencenodicarboxamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- bis[2- (dimetilamino) etil]- N,N´- dimetil- 1,3- bencenodicarboxamida;

4- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N,N`- dimetil- N,N´- bis[2- (metiloxi) etil]- 1,3- bencenodicarboxamida;

(3R, 6R) - 1- {[2,4- bis(4- metil- 1- piperazinil) carbonil]fenil}]metil) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (hidroximetil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[4- (metilsulfonil) - 2- (4- morfolinilcarbonil) fenil]metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- [(4- metil- 1- piperazinil) - carbonil) - 4- (metilsulfonil) fenil]metil}- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- N- [2- (metiloxi) etil]- 5- (metilsulfonil) benzamida;

N- [2- (dietilamino) etil]- 2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- metil- 5- (metilsulfonil) benzamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- [(4- metilsulfonil) - 2- {[(2S) - 2- (1- pirrolidinilmetil) - 1- pirrolidinil]carbonil}fenil) metil]- 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- (2- hidroxietil) bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(4- metilhexahidro- 1H- 1,4- diazepin- 1- il) sulfonil]fenil}metil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}- N- {[(2R) - 1- etil- 2- pirrolidin]metil}bencenosulfonamida;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[(3S) - 3- (dimetilamino) - 1- pirrolidinil]- sulfonil}fenil) metil]- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[(3R) - 3- (dimetilamino) - 1- pirrolidinil]- sulfonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- metiletil) - 2,5- dioxo- 1- piperazinil]- metil}bencenosulfonamida;

N- [(2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) sulfonil]glicina.

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- ({2- [(1- metiletil) sulfonil]- fenil}metil) - 2,5- piperazinadiona;

(3R, 6R) - 1- [(2- aminofenil) metil- 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 2,5- piperazinadiona;

ácido formico - N- (2- {[(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 2,5- dioxo- 1- piperazinil]- metil}fenil) - N^2, N^2- dimetilglicinanida (1:1) ;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- imidazol- i1) fenil]- metil}- 2,5- piperazinadiona;

ácido formico - (3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- [(2- {[3- dimetilamino) propil]- sulfonil}fenil) metil]- 6- (1- etilpropil) - 2,5- piperazinadiona (1:1) ;

(3R, 6R) - 6- ciclopentil- 3- (2,3- dihidro- 1H- inden- 1- {[4- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 1- {[(1,5- dimetil- 1H- pirazol- 4- i1) - metil]- 6- (1- etilpropil) - 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (2- metilpropil) - 1- {[2- (metilsulfonil) fenil]- metil}- 2,5- piperazinadiona;

(3R, 6R) - 3- (2,3- dihidro- 1H- inden- 2- il) - 6- (1- etilpropil) - 1- {[2- (1H- pirazol- 1- il) fenil]- metil}- 2,5- piperazinadiona;

20. Una composición farmacéutica que comprende al menos una entidad química que comprende al menos un compuesto de la Fórmula (IA) y derivados farmacéuticamente aceptables del mismo según cualquiera de las reivindicaciones 2 a 19 y un vehiculo o diluyente farmacéuticamente aceptable.

21. Al menos una entidad química que comprende un compuesto de la Fórmula (IA) y derivados fisiológicamente aceptables del mismo según cualquiera de las reivindicaciones 2 a 19 para utilizar en terapia.

22. Al menos una entidad química que comprende un compuesto de la Fórmula (IA) y derivados fisiológicamente aceptables del mismo según cualquiera de las reivindicaciones 2 a 19 para utilizar en el tratamiento o prevención de enfermedades o condiciones mediadas a través de la acción de oxitocina.

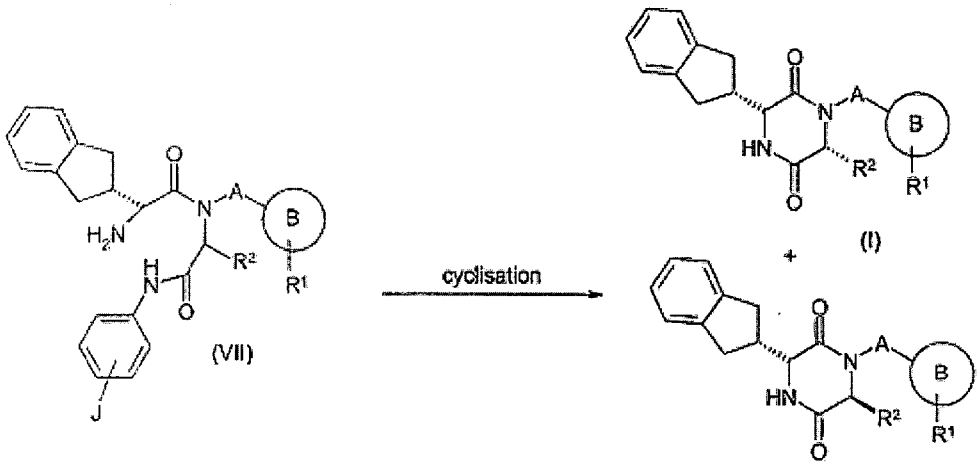
23. El uso de al menos una entidad química que comprende un compuesto de la Fórmula (IA) y derivados fisiológicamente aceptables del mismo según cualquiera de las reivindicaciones 2 a 19 en la fabricación de un medicamento para antagonizar los efectos de oxitocina sobre el receptor de oxitocina.

24. El uso de al menos una entidad química que comprende un compuesto de la Fórmula (IA) y derivados fisiológicamente aceptables del mismo según cualquiera de las reivindicaciones 2 a 19 en la fabricación de un medicamento para el tratamiento de una o más enfermedades o condiciones seleccionadas de trabajo de parto pre- término, dismenorrea y endometriosis.

25. Un método para tratar o prevenir enfermedades o condiciones mediadas a través de la acción de oxitocina, el cual comprende la administración a un mamífero en necesidad del mismo de una cantidad efectiva de al menos una entidad química que comprende un compuesto de la Fórmula (IA) y derivados fisiológicamente aceptables del mismo según cualquiera de las reivindicaciones 2 a 19.

26. Un método según la reivindicación 25 en donde la enfermedad o condición es seleccionada entre trabajo de parto pre- término, dismenorrea y endometriosis.

27. Un proceso para la preparación de un compuesto de la Fórmula (I) según la reivindicación 1 que comprende ciclización de un compuesto de la Fórmula (VII) , en donde A, B, R1 y R2 son como se definieron para la Fórmula (I) , y J es un sustituyente opcional, opcionalmente en la presencia de un ácido o base apropiada.


H2N
O
N
A
B
R2
R1
H
N
O
J
(VII)
cyclisation
HN
(I)
+

PATENT COOPERATION TREATY

PCT

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
GLAXO GROUP LIMITED		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB2005/005007	22/12/2005	23/12/2004
Applicant		
FES/PB61211		

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

This international search report consists of a total of 4 sheets.

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

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   1,6-SUBSTITUTED (3R,6R)-3-(2,3-DIHYDRO-1H-INDEN-2-YL)-2,5-PIPERAZINEDIONE DERIVATIVES AS OXYTOCIN RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PRE-TERM LABOUR, DYSMENORRHEA AND ENDOMETRIOSIS

5. With regard to the **abstract**,
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

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Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to compound S of Formula (I)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2005/005007

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D241/08 A61P15/06

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)
C07D 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.
A	WO 03/053443 A (GLAXO GROUP LIMITED) 3 July 2003 (2003-07-03) cited in the application the whole document	1-27
P,A	WO 2005/000840 A (GLAXO GROUP LIMITED) 6 January 2005 (2005-01-06) cited in the application the whole document	1-27

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2006	03/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cortés, J

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INTERNATIONAL SEARCH REPORT

.rnational application No.
PCT/GB2005/005007

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of 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

...ormation on patent family members

Ir ional application No
PCT/GB2005/005007

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03053443 A	03-07-2003	AU 2002364304 A1	09-07-2003
		BR 0215277 A	14-12-2004
		CA 2471355 A1	03-07-2003
		CN 1606443 A	13-04-2005
		EP 1458393 A1	22-09-2004
		HU 0500136 A2	30-05-2005
		JP 2005517663 T	16-06-2005
		MX PA04006033 A	27-09-2004
		US 2005148572 A1	07-07-2005
		ZA 200404326 A	26-07-2005
WO 2005000840 A	06-01-2005	AU 2004251868 A1	06-01-2005
		CA 2530310 A1	06-01-2005

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/005007	22.12.2005	23.12.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07D241/08 A61P15/06

Applicant
FES/PB61211

1. This opinion contains indications relating to the following items:

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

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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

For further options, see Form PCT/ISA/220.

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

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Cortés, J Telephone No. +49 89 2399-8206

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/005007

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

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

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in electronic form.

   ☐ furnished subsequently to this Authority for the purposes of search.

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

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/005007

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

☐ the entire international application

☒ claims Nos. 25,26

because:

☒ the said international application, or the said claims Nos. 25,26 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

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

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

☒ no international search report has been established for the whole application or for said claims Nos. -

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/005007

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

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-24,27
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2005/005007

Re Item III

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

Claims 1-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion with regard to the industrial applicability will be formulated for these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: WO 03/053443 A (GLAXO GROUP LIMITED) 3 July 2003 (2003-07-03) cited in the application

Novelty (Article 33(2) PCT)

The present compounds differ from the compounds in D1 in the group -A-B-R1.

Inventive Step (Article 33(3) PCT)

The problem of the invention was the provision of new oxytocin receptor inhibitors.

D1 discloses structurally related oxytocin receptor inhibitors and could be regarded as the closest prior art.

The present compounds are not anticipated or suggested by D1.

Clarity (Article 6 PCT)

The terms "chemical entities" and "derivatives" in the claims are unclear.

The expressions containing the term "chemical entities should be deleted.

The term "derivatives" could be replaced by the structurally defined terms given in the description (page 10, lines 39-40), i.e. "salt, solvate, ester or carbamate".

Re Item VI

Certain documents cited

D2: WO 2005/000840 A (GLAXO GROUP LIMITED) 6 January 2005 (2005-01-06) cited in the application, P-document

The present compounds differ from the compounds in D2 in the group -A-B-R1 and are not suggested by D2.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-062231- -00000-0000

Fecha: 2007-06-20 16:42:44 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 349

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [4] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [4]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [4]
- Descripción de la invención [4]
- Dibujos de ser estos pertinentes [4]
- Comprobante de pago de las tasas establecidas [4]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

20 JUN. 2007

Fecha

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