CSA047342

INVENTAR

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Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08-24576

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO DERIVADOS DE PIRIDINA Y SU USO EN EL TRATAMIENTO DE TRASTORNOS PSICOTICOS

SOLICITANTE: SMITHKLINE BEECHAM CORPORATION

DIRECCIÓN: One Franklin Plaza, P.O Box 7929, Philadelphia, PA 19101 E.U.A.

A61K 31/485 ; 31/538

APODERADO: CARLOS R. OLARTE

BOGOTÁ 07 de Marzo de 2008

P2008/000038

SS

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-024576 -00000-0000
Fecha: 2008-03-07 16:35:21 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 666

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000038**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SMITHKLINE BEECHAM CORPORATION
Dirección: One Franklin Plaza, PO Box 7929, Philadelphia, Pennsylvania 19101 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Estados Unidos de América.
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

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IDENTIFICACIÓN
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Número 79782747Bta
TP 74.295

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Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2006/008845 Fecha Septiembre 7, 2006

Publicación Internacional No. WO 2007/028654 Fecha Marzo 15, 2007

(6) **Título (54)** **DERIVADOS DE PIRIDINA Y SU USO EN EL TRATAMIENTO DE TRASTORNOS PSICOTICOS**

Clasificación Internacional (51) C07D 513/04, C07D 487/04, C07D 498/04, A61K 31/4985, A61K 31/5383, A61K 31/542, A61K 31/4439, A61K 31/551, A61P 25/00

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GB	Septiembre 9, 2005	0518472.6
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(0) **ANEXOS**

2

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto Copia simple. Ver expediente No. 06.078.318
- [ ] 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

(1) **FIGURA CARACTERÍSTICA:**

(2) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

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38

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 20,062
FECHA : MARZO 7 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 666

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	106977	06/03/2008	6,473,000.00

***** 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	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SMITHKLINE BEECHAM CORPORATION

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 certificando que Peter John Giddings es apoderado de Smithkline Beecham Corporation, 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. G229470
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

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

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

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Ingles
Resolución No. 2117 del 7 Oct 1987

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 "P. Giddings" 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 corporación denominada **"SMITHKLINE BEECHAM CORPORATION"**, corporación legalmente constituída y existente de acuerdo con las leyes del Estado de Pensilvania, Estados Unidos de América, con domicilio social en 1, Franklin Plaza, Philadelphia, Pensilvania 19101, Estados Unidos de América;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el 11 de julio de 2002, copia del cual he tenido a la vista.

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 trece de agosto del año dos mil tres.

SCRIVENER NOTARIES

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

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

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

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

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 **G229470**

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.

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Power of Attorney

The undersigned,

SmithKline Beecham Corporation

domiciled in

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

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,

SmithKline Beecham Corporation

domiciliado en

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

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,Pais: Brentford, Middlesex, England

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

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C07D 498/04 (2006.01) *A61K 31/551* (2006.01)
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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, PO Box 7929, Philadelphia, Pennsylvania 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALVARO, Giuseppe** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **ANDREOTTI, Daniele** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **BELVEDERE, Sandro** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **DI FABIO, Romano** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **FALCHI, Alessandro** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **GIOVANNINI, Riccardo** [IT/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT).

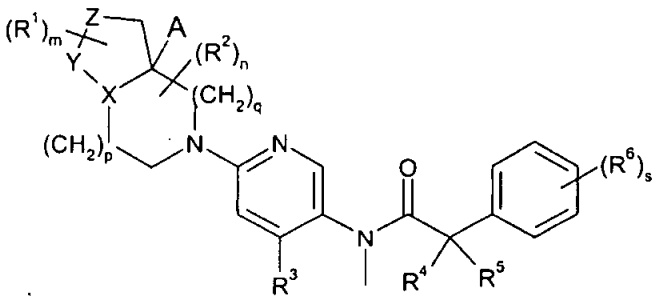
(74) Agent: **DOLTON, Peter**; GlaxoSmithKline, Corporate Intellectual Property, Cn925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

[Continued on next page]

(54) Title: PYRIDINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF PSYCHOTIC DISORDERS



(I)

(57) **Abstract:** There are provided according to the invention novel compounds of formula (I) or a pharmaceutically acceptable salt thereof: (I) wherein: X represents a nitrogen atom; Y represents $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ or $-C(=O)-$; Z represents $-C(H_2)-$, $-S(O_2)-$, $-N(R^7)-$, or an oxygen or sulphur atom; A represents hydrogen or $-CH_2OH$; R^7 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, -COR7 or -SO2R7; R^1 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, =O, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, hydroxyl or $-CH_2OH$; m represents an integer from 0 to 3; R^2 represents halogen, =O, C_{1-6}alkyl (optionally substituted by one or more hydroxyl groups), $-COOR^7$, $-CONR^7R^8$, C_{1-6} alkoxy, haloC_{1-6} alkyl, haloC_{1-6}alkoxy or C_{1-6} alkyloC$_{1-6}$ alkyl; n represents an integer from 0 to 3; p and q independently represent an integer from 0 to 2; R^3 represents an -aryl, -heteroaryl, -heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or -heterocyclyl-heterocyclyl group, all of which may be optionally substituted by one or more (e.g. 1, 2 or 3) halogen, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), C_{3-8}cycloalkyl, C_{1-6} alkoxy, hydroxyl, haloC_{1-6}alkyl, haloC_{1-6} alkoxy, cyano, $-S-C_{1-6}$ alkyl, $-SO-C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, $-NR^7COC_{1-6}$ alkyl, $-NR^7SO_2-C_{1-6}$alkyl, C_{1-6} alkyl-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ or $-SO_2NR^7R^8$ groups; R^4 and R^5 independently represent C_{1-6} alkyl, or R^4 and R^5 together with the carbon atom to which they are attached may together form a C_{3-8}cycloalkyl group; R6 represents halogen, C_{1-6} alkyl, C_{3-8}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy; s represents an integer from 0 to 4; R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl or C_{3-8}cycloalkyl; or solvates thereof.

WO 2007/028654 A1

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

9

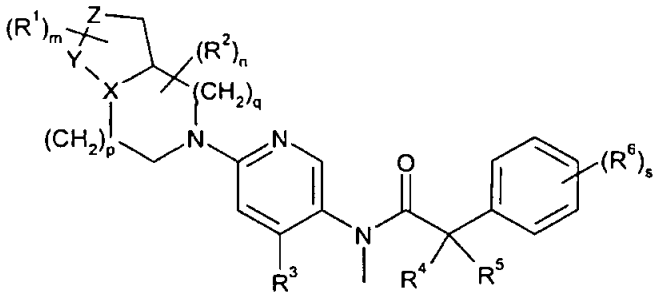
10

PYRIDINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF PSYCHOTIC DISORDERS

The present invention relates to novel nitrogen containing bicyclic derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of psychotic disorders, in particular schizophrenia.

WO 2005/002577 (F. Hoffmann-La Roche AG) describes a series of pyridine derivatives which are clamed to be dual NK1/NK3 antagonists for treating schizophrenia.

The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X represents a nitrogen or sulphur atom;

Y represents $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ or $-C(=O)-$;

Z represents $-C(H_2)-$, $-S(O_2)-$, $-N(R^z)-$, or an oxygen or sulphur atom;

R^z represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-COR^7$ or $-SO_2R^7$;

R^1 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, =O, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;

m represents an integer from 0 to 3;

R^2 represents halogen, =O, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), $-COOR^7$, $-CONR^7R^8$, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;

n represents an integer from 0 to 3;

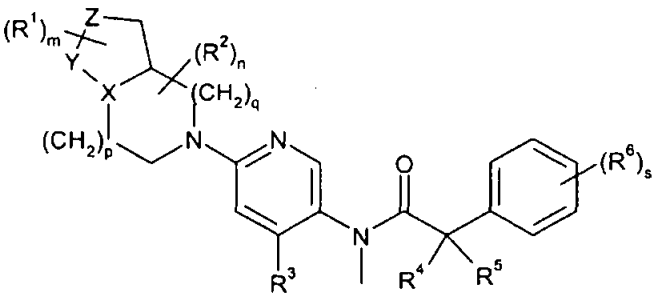
p and q independently represent an integer from 0 to 2;

R^3 represents an –aryl, -heteroaryl, -heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or –heterocyclyl-heterocyclyl group, all of which may be optionally substituted by one or more (e.g. 1, 2 or 3) halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, hydroxyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, cyano, $-S-C_{1-6}$ alkyl, $-SO-C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, NR^7COC_{1-6} alkyl, $NR^7SO_2-C_{1-6}$ alkyl, C_{1-6} alkyl-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ or $-SO_2NR^7R^8$ groups;

R^4 and R^5 independently represent C_{1-6} alkyl, or R^4 and R^5 together with the carbon atom to which they are attached may together form a C_{3-8} cycloalkyl group;

R^6 represents halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;
s represents an integer from 0 to 4;
R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;
or solvates thereof.

In a further aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:

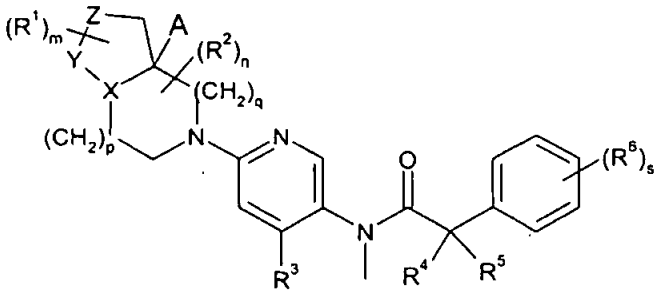


(I)

wherein:
X represents a nitrogen atom;
Y represents $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ or $-C(=O)-$;
Z represents $-C(H_2)-$, $-S(O_2)-$, $-N(R^z)-$, or an oxygen or sulphur atom;
R^z represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-COR^7$ or $-SO_2R^7$;
R^1 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, =O, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;
m represents an integer from 0 to 3;
R^2 represents halogen, =O, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), $-COOR^7$, $-CONR^7R^8$, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;
n represents an integer from 0 to 3;
p and q independently represent an integer from 0 to 2;
R^3 represents an –aryl, -heteroaryl, -heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or –heterocyclyl-heterocyclyl group, all of which may be optionally substituted by one or more (e.g. 1, 2 or 3) halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, hydroxyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, cyano, $-S-C_{1-6}$ alkyl, $-SO-C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, NR^7COC_{1-6} alkyl, $NR^7SO_2-C_{1-6}$ alkyl, C_{1-6} alkyl-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ or $-SO_2NR^7R^8$ groups;
R^4 and R^5 independently represent C_{1-6} alkyl, or R^4 and R^5 together with the carbon atom to which they are attached may together form a C_{3-8} cycloalkyl group;
R^6 represents halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;
s represents an integer from 0 to 4;
R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

or solvates thereof.

In another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X represents a nitrogen atom;

Y represents $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ or $-C(=O)-$;

Z represents $-C(H_2)-$, $-S(O_2)-$, $-N(R^z)-$, or an oxygen or sulphur atom;

A represents hydrogen or $-CH_2OH$;

R^z represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-COR^7$ or $-SO_2R^7$;

R^1 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, =O, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, hydroxyl or $-CH_2OH$;

m represents an integer from 0 to 3;

R^2 represents halogen, =O, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), $-COOR^7$, $-CONR^7R^8$, C_{1-6} alkoxy, haloC_{1-6} alkyl, haloC_{1-6} alkoxy or C_{1-6}alkylOC_{1-6}alkyl;

n represents an integer from 0 to 3;

p and q independently represent an integer from 0 to 2;

R^3 represents an –aryl, -heteroaryl, -heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or –heterocyclyl-heterocyclyl group, all of which may be optionally substituted by one or more (e.g. 1, 2 or 3) halogen, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), C_{3-8} cycloalkyl, C_{1-6} alkoxy, hydroxyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, cyano, $-S-C_{1-6}$ alkyl, $-SO-C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, $-NR^7COC_{1-6}$ alkyl, $-NR^7SO_2-C_{1-6}$ alkyl, C_{1-6} alkyl-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ or $-SO_2NR^7R^8$ groups;

R^4 and R^5 independently represent C_{1-6} alkyl, or R^4 and R^5 together with the carbon atom to which they are attached may together form a C_{3-8} cycloalkyl group;

R^6 represents halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;

s represents an integer from 0 to 4;

R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

or solvates thereof.

The term 'C_{1-6} alkyl' as used herein as a group or a part of the group refers to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like.

The term 'C_{1-6} alkoxy' as used herein refers to an –O-C_{1-6} alkyl group wherein C_{1-6} alkyl is as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy and the like.

The term 'C_{3-8} cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like.

The term 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom.

The term 'haloC_{1-6} alkyl' as used herein refers to a C_{1-6} alkyl group as defined herein wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include fluoroethyl, trifluoromethyl or trifluoroethyl and the like.

The term 'haloC_{1-6} alkoxy' as used herein refers to a C_{1-6} alkoxy group as herein defined wherein at least one hydrogen atom is replaced with halogen. Examples of such groups include difluoromethoxy or trifluoromethoxy and the like.

The term 'aryl' as used herein refers to a C_{6-12} monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl or tetrahydronaphthalenyl and the like.

The term 'heteroaryl' as used herein refers to a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of such fused aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

The term 'heterocyclyl' refers to a 4-7 membered monocyclic ring or a fused 8-12 membered bicyclic ring which may be saturated or partially unsaturated containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur. Examples of such monocyclic rings include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and the like. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine, tetrahydroisoquinolinyl and the like.

In one embodiment, p and q both represent 1, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is hexahydropyrrolopyrazinyl (e.g. hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl).

In an alternative embodiment, p and q both represent 1, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents an oxygen atom, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is hexahydropyrazino-oxazinyl (e.g. hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl).

In a further alternative embodiment, p and q both represent 1, X represents a nitrogen atom, Y represents -$S(O_2)$- and Z represents -$C(H_2)$-, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is dioxidohexahydroisothiazolopyrazinyl (e.g. 1,1-dioxidohexahydro-5*H*-isothiazolo[2,3-*a*]pyrazin-5-yl).

In a yet further alternative embodiment, p and q both represent 1, X represents a nitrogen atom, Y represents -C(=O)- and Z represents -$C(H_2)$-, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is oxohexahydropyrrolopyrazinyl (e.g. 6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl).

In a yet further alternative embodiment, p represents 1, q represents 2, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is octahydropyrrolodiazepinyl (e.g. octahydro-3*H*-pyrrolo[1,2-*d*][1,4]diazepin-3-yl).

In a yet further alternative embodiment, p represents 2, q represents 1, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is oxahexahydropyrrolodiazepinyl (e.g. oxohexahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-2(3*H*)-yl).

In a yet further alternative embodiment, p and q both represent 1, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents $-S(O_2)-$, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is dioxidohexahydropyrazinothiazinyl (e.g. 2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl).

In a yet further embodiment, p and q both represent 1, X represents nitrogen, Y represents $(-C(H_2)-)_2$ and Z represents $-N(R^z)-$, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is octahydropyrazinopyrazinyl (e.g. octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl).

In a yet further embodiment, when p represents zero and q represent 1, X represents nitrogen, Y represents $-C(H_2)-$ and Z represents $-C(H_2)-$, for example, the bicyclic moiety attached to the pyridinyl ring in formula (I) is oxotetrahydropyrroloimidazolyl (e.g. oxotetrahydro-1H-pyrrolo[1,2-*c*]imidazol-2(3*H*)-yl).

In one embodiment, m represents 0.

In another embodiment, m represents 1.

In one embodiment, when m represents 1, R^1 represents =O, hydroxyl, $-CH_2OH$.

In one embodiment, n represents 0 or 1.

In a further embodiment, when n represents 1, R^2 represents =O or C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups; e.g. $-CH_2-OH$ or CH_3).

In another embodiment, when n represents 1, R^2 represents C_{1-6}alkylOC_{1-6}alkyl (e.g. $-CH_2OCH_3$) or haloC_{1-6} alkyl (e.g. $-CH_2F$).

In a yet further embodiment, when n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group (e.g. $-CH_2-OH$).

In one embodiment A represents hydrogen.

In another embodiment A represents $-CH_2OH$.

In one embodiment, p and q either both represent 1 or one of p or q represents 1 and the other of p or q represents 2. In a further embodiment, p and q both represent 1.

In a yet further embodiment when q represents 1, p represents 0.

In one embodiment, R^7 represents C_{1-6}alkyl (e.g. methyl).

In one embodiment, when Z represents $-N(R^z)-$, R^z represents hydrogen, C_{1-6} alkyl, $-COR^7$ or $-SO_2R^7$.

In another embodiment, R^z represents $-COR^7$.

In another embodiment, R^z represents C_{1-6}alkyl or $-SO_2R^7$.

In a yet further embodiment when R^z represents $-COR^7$, R^7 represents C_{1-6}alkyl (e.g. methyl).

In a yet further embodiment when R^z represents $-SO_2R^7$, R^7 represents C_{1-6}alkyl (e.g. methyl).

In one embodiment, R^3 represents –aryl (e.g. phenyl) mono substituted by a halogen (e.g. 2-chlorine) or C_{1-6} alkyl (e.g. 2-methyl) group or –aryl (e.g. phenyl) di substituted by a halogen (e.g. 4-fluorine) and C_{1-6} alkyl (e.g. 2-methyl) group.

In a further embodiment, R^3 represents –aryl (e.g. phenyl) di substituted by a halogen (e.g. 4-fluorine) and C_{1-6} alkyl (e.g. 2-methyl) group (e.g. 4-fluoro-2-methylphenyl).

In a further embodiment R^3 represents –aryl (e.g.phenyl) monosubstitued by C_{1-6}alkyl substituted by one or more hydroxyl groups (e.g. $-CH_2OH$) or –aryl (e.g. phenyl) di substituted by a halogen (e.g. 2-chloro-4-fluorophenyl) or a halogen (e.g. 5-fluorine) and a C_{1-6} alkyl (e.g. 2-methyl) group (e.g. 5-fluoro-2-methylphenyl).

In a further embodiment R^3 represents –heteroaryl (e.g.pyridinyl) monosubstitued by C_{1-6}alkyl (e.g. 6-methylpyridin-3-yl)) or –heteroaryl (e.g. pyridinyl) di substituted by a halogen (e.g. 4-fluorine) and a C_{1-6} alkyl (e.g. 2-methyl) group (e.g. 4-fluoro-2-methylpyridin-3-yl).

In one embodiment, R^4 and R^5 both represent C_{1-6} alkyl (e.g. methyl), or R^4 and R^5 together with the carbon atom to which they are attached together form a C_{3-8} cycloalkyl (e.g. cyclopropyl) group. In a further embodiment, R^4 and R^5 both represent C_{1-6} alkyl (e.g. methyl).

In a yet further embodiment R^4 and R^5 together with the carbon atom to which they are attached together form a C_{3-8} cycloalkyl (e.g. cyclopropyl) group.

In one embodiment, s represents 2 and both R^6 groups are haloC_{1-6} alkyl (such as trifluoromethyl groups, e.g. 3,5-bis(trifluoromethyl)).

In one embodiment, when p and q both represent 1, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents an oxygen atom, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, R^3 represents –aryl di substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl and s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl.

In one embodiment, when p and q both represent 1, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents $-S(O_2)-$, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, R^3 represents –aryl di substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl and s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl.

In one embodiment, when p and q both represent 1, X represents nitrogen, Y represents $(-C(H_2)-)_2$ and Z represents $-N(R^z)-$, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, R^3 represents –aryl di substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl and s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl.

In a yet further embodiment, p and q both represent 1, n and m both represent 0, A represents hydrogen, X represents nitrogen, Y represents $(-C(H_2)-)_2$, Z represents $-N(R^z)-$, R^3 represents –aryl substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl, s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl and R^z represents $-COR_7$, wherein R_7 is C_{1-6}alkyl.

Compounds according to the invention include examples E1-E33 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds according to the invention further include examples E34-E40 as shown below, or a pharmaceutically acceptable salt thererof.

Compounds according to the invention further include examples E41-E104 as shown below, or a pharmaceutically acceptable salt thererof.

In one embodiment, the invention provides a compound selected from the group consisting of:

2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,

2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,

2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,
N-[6-[(3*S*)-8-acetyl-3-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the invention provides 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or a pharmaceutically acceptable salt thereof.

In a further embodiment, the invention provides *N*-[6-[(9a*S or 9aR*)-8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (Enantiomer 2) or a pharmaceutically acceptable salt thereof, wherein "Enantiomer 2" means a single enantiomer of unknown absolute stereochemistry prepared according to Example 72 described hereinbelow.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

As used herein, the term "salt" refers to any salt of a compound according to the present invention prepared from an inorganic or organic acid or base, quaternary ammonium salts and internally formed salts. Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compounds. Such salts must clearly have a physiologically acceptable anion or cation. Suitably physiologically acceptable salts of the compounds of the present invention include acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and with organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, camphorsulfuric, isothionic, mucic, gentisic, isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example benzenesulfonic and p-toluenesulfonic, acids; base addition salts formed with alkali metals and alkaline earth metals and organic bases such as N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine and procaine; and internally formed salts. Salts having a non-physiologically acceptable anion or cation are within the scope of the invention as useful intermediates for the preparation of

physiologically acceptable salts and/or for use in non-therapeutic, for example, *in vitro*, situations.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O, 31P, 32P, 35S, 18F, 36Cl, 123I and 125I.

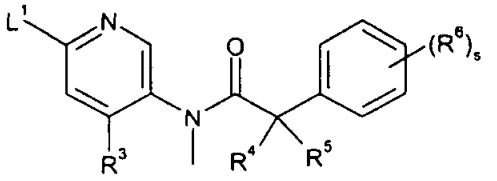
Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H, and carbon-14, i.e., 14C, isotopes are particularly preferred for their ease of preparation and detectability. 11C and 18F isotopes are particularly useful in PET (positron emission tomography), and 125I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. * indicates a stereocentre of fixed but unknown stereochemistry i.e. either *R* or *S* stereochemistry. Diastereoisomer 1 or Diastereoisomer 2 means a compound of the invention or an intermediate thereof as a single diastereoisomer whose absolute configuration at one stereocentre was not determined. Enantiomer 1 or Enantiomer 2 means a compound of the invention or an intermediate thereof as a single enantiomer whose absolute configuration was not determined. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

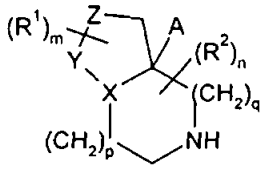
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(a) reacting a compound of formula (II)



(II)

wherein R^3, R^4, R^5, R^6 and s are as defined above and L^1 represents a suitable leaving group such as a halogen atom (e.g. chlorine), with a compound of formula (III)



(III)

or an optionally protected derivative thereof, wherein R^1, R^2, m, n, p, q, X, Y, Z and A are as defined above; optionally thereafter followed by

(b) deprotecting a compound of formula (I) which is protected; and

(c) interconversion to other compounds of formula (I).

When p and q both represent 1, X represents a nitrogen atom, Y represents -C(=O)- and Z represents -$C(H_2)$-, process (a) may be performed in the presence of a suitable base such as potassium carbonate and a suitable solvent such as DMSO at a suitable temperature, such as 150-180°C.

When p and q both represent 1, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, process (a) may be performed in the presence of a suitable base such as potassium carbonate and a suitable solvent such as DMSO at a suitable temperature, such as 180°C by microwave irradiation.

When p and q both represent 1, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group (e.g. $-CH_2$-OH), process (a) may be performed in the presence of a suitable base such as potassium tertbutoxide or caesium carbonate, a suitable solvent such as DMSO, a suitable catalyst such as bis(dibenzylideneacetone)palladium (0.05eq) a suitable ligand such as dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (0.125eq) at a suitable temperature, such as 120°C by microwave irradiation; or in the alternative, process a) may be performed in the presence of a suitable base such as potassium carbonate and a suitable solvent such as DMSO at a suitable temperature, such as between 110 and 160°C.

Alternatively, when p and q both represent 1, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group (e.g. $-CH_2$-OH), process (a) may be performed on the derivative wherein the hydroxyl group of R^2 is protected as an O-TBDMS derivative, in a suitable solvent such as toluene, in the presence of a suitable catalyst such as bis-tri –tert-butylphosphine palladium, a suitable base such as aqueous sodium hydroxide and a suitable phase transfer catalyst such as aqueous cetyltrimethylammonium chloride at a temperature such as 80-95°C. This process can be followed by removal of theTBDMS protecting group using tetrabutylammonium fluoride in a suitable solvent such as THF, or hydrochloric acid in a suitable solvent such as methanol.

Alternatively, when p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents an oxygen atom, -$S(O_2)$- or $-N(R^z)$, n represents 1 and R^2 represents C_{1-6} alkyl substituted by a hydroxyl group (e.g. $-CH_2$-OH) process (a) may be performed on the derivative wherein the hydroxyl group of R^2 is protected as an O-TBDMS derivative in a suitable solvent such as toluene, in the presence of a suitable catalyst such as bis-tri –tert-butylphosphine palladium, a suitable base such as aqueous sodium hydroxide and a suitable phase transfer catalyst such as aqueous hexadecyltrimethylammonium chloride at a temperature such as 80-95°C. This process can be followed by removal of theTBDMS protecting group using tetrabutylammonium fluoride in a suitable solvent such as THF, or hydrochloric acid in a suitable solvent such as methanol.

Alternatively, when p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents an oxygen atom or $-N(R^z)$, n represents 1 and R^2 represents C_{1-6} alkyl or haloC_{1-6} alkyl, process (a) may be performed in a suitable solvent such as toluene, in the presence of a suitable catalyst such as bis-tri –tert-butylphosphine palladium, a suitable base such as aqueous sodium hydroxide and a suitable phase transfer catalyst such as aqueous hexadecyltrimethylammonium chloride at a temperature such as 80-95°C.

Alternatively, when p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents $-N(R^z)$, n represents 0, m represents 1, and R^1 represents $-CH_2$-OH process (a) may be performed in the presence of a suitable base such as potassium carbonate and a suitable solvent such as DMSO at a suitable temperature, such as 150°C.

When p and q both represent 1, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents an oxygen atom or when p and q both represent 1, X represents a nitrogen atom, Y represents -$S(O_2)$- and Z represents -$C(H_2)$-, or when p represents 1, q represents 2, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, or when p represents 2, q represents 1, X represents a nitrogen atom, Y represents -$C(H_2)$-, Z represents -$C(H_2)$-, n represents 1 and R^2 represents =O, process (a) may typically be performed in the presence of a suitable base such as potassium carbonate, a suitable

reaction promoter such as copper iodide in a suitable solvent such as DMSO at a suitable temperature such as 150°C by microwave irradiation.

When p represents 1, q represents 1, X represents a nitrogen atom, Y represents $-C(H_2)-$, Z represents $-C(H_2)-$, n represents 1 and R^2 represents =O, process (a) may typically be performed in the presence of N,N'-dimethylethylenediamine, a suitable base such as caesium carbonate, a suitable reaction promoter such as copper iodide in a suitable solvent such as dioxane, at a suitable temperature such as 80-120°C.
When p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents NH, process (a) may be performed in the presence of a suitable base such as potassium carbonate and a suitable solvent such as DMSO at a suitable temperature, such as 130°C.

In process (b), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulfonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

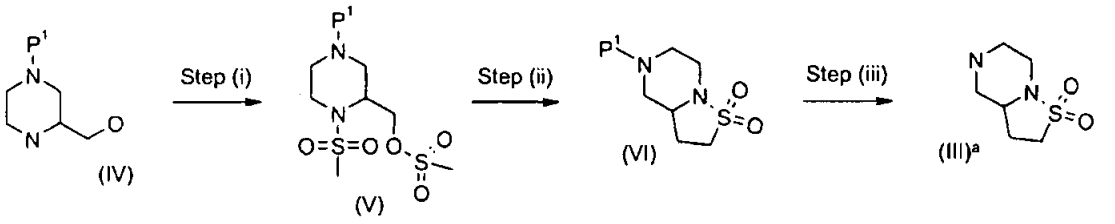
Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis, amide bond formation or transition metal mediated coupling reactions. Examples of transition metal mediated coupling reactions useful as interconversion procedures include the following: Palladium catalysed coupling reactions between organic electrophiles, such as aryl halides, and organometallic reagents, for example boronic acids (Suzuki cross-coupling reactions); Palladium catalysed amination and amidation reactions between organic electrophiles, such as aryl halides, and nucleophiles, such as amines and amides; Copper catalysed amidation reactions between organic electrophiles (such as aryl halides) and nucleophiles such as amides; and Copper mediated coupling reactions between phenols and boronic acids.

For example, compounds of formula (I) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$, Z represents $N(R^z)$, and R^z represents COR^7 may be prepared from compounds of formula (I) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents NH, *via* acylation using the appropriate acid chloride, in the

presence of a suitable base, such as triethylamine, in a suitable solvent, such as dichloromethane. Similarly, compounds of formula (I) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$, Z represents $N(R^z)$, and R^z represents SO_2R^7 may be prepared from compounds of formula (I) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents NH, *via* sulfonylation using the appropriate sulfonyl chloride in the presence of a suitable base, such as triethylamine, in a suitable solvent, such as dichloromethane. Compounds of formula (I) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$, Z represents $N(R^z)$, and R^z represents C_{1-6}alkyl, may be prepared from compounds of formula (I) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents NH, *via* reductive alkylation employing the appropriate aldehyde in a suitable solvent, such as acetonitrile, followed by treatment with sodium triacetoxyborohydride. Compounds of formula (I) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents C_{1-6}alkylOC_{1-6}alkyl, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$, Z represents $-S(O)_2-$, may be prepared from compounds of formula (I) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents C_{1-6}alkyl substituted by one hydroxyl group, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$, and Z represents $-S(O)_2$ *via* alkylation employing a suitable alkyl halide in the presence of a base, such as sodium hydride, in a suitable solvent such as THF.

Compounds of formula (II) may be prepared in accordance with the methodology provided in WO 2005/002577.

Compounds of formula (III) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $-S(O_2)-$ and Z represents $-C(H_2)-$ may be prepared in accordance with the following scheme:



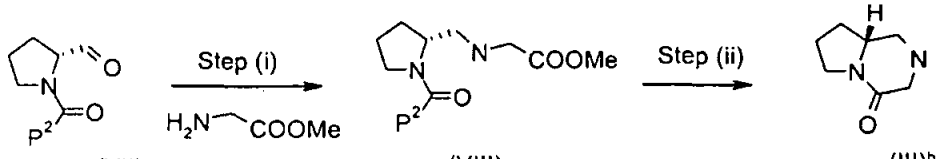
wherein P^1 represents a suitable protecting group such as Boc.

Step (i) typically comprises reacting a compound of formula (IV) with methanesulfonyl chloride in the presence of a suitable solvent such as dichloromethane and a suitable base such as triethylamine.

Step (ii) typically comprises reacting a compound of formula (V) with sec-butyllithium in the presence of a suitable solvent such as tetrahydrofuran.

Step (iii) typically comprises a deprotection reaction, for example, when P^1 represents Boc said deprotection reaction may typically comprise reacting a compound of formula (VI) with a mixture of dichloromethane and trifluoroacetic acid.

Compounds of formula (III) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents =O, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$- may be prepared in accordance with the following scheme:



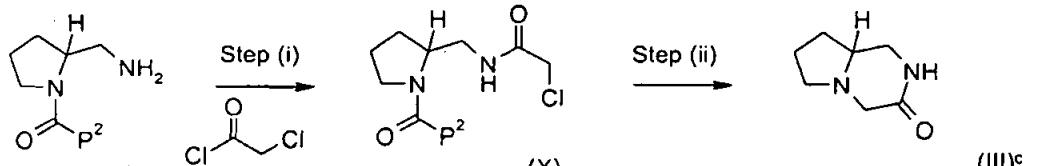
(VII) (VIII) (III)^b

wherein P^2 represents a suitable protecting group such as t-butoxy.

Step (i) typically comprises reaction in the presence of sodium triacetoxyborohydride and a suitable acid, such as hydrochloric acid.

Step (ii) typically comprises a deprotection reaction, for example, when P^2 represents t-butoxy said deprotection reaction may typically comprise reacting a compound of formula (VIII) with a mixture of dichloromethane and trifluoroacetic acid, followed by purification on a SCX (Strong Cationic Exchange) silica cartridge and heating the basic methanolic fractions at a suitable temperature, such as 40°C.

Compounds of formula (III) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents =O, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$- may also be prepared in accordance with the following scheme:



(IX) (X) (III)^c

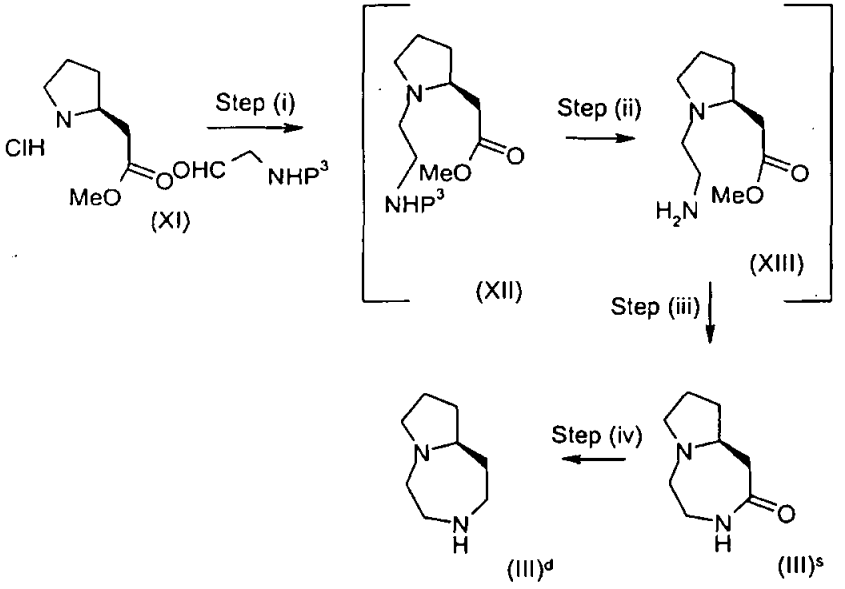
wherein P^2 represents a suitable protecting group such as t-butoxy.

Step (i) typically comprises reaction with chloroacetyl chloride in the presence of a suitable base such as N,N-diisopropylethylamine in dichloromethane.

Step (ii) typically comprises a deprotection reaction, for example, when P^2 represents t-butoxy said deprotection reaction may typically comprise reacting a compound of formula (X) with a mixture of dichloromethane and trifluoroacetic acid, followed by purification on a

SCX (Strong Cationic Exchange) silica cartridge and heating of the resulting intermediate with a base such as sodium carbonate in acetonitrile at a suitable temperature, such as 60°C.

Compounds of formula (III) wherein p represents 1, q represents 2, m represents 0, n represents 1, R^2 represents =O, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-, or wherein p represents 1, q represents 2, m and n both represent 0, X represents a nitrogen atom, Y represents -$C(H_2)$- and Z represents -$C(H_2)$-may be prepared in accordance with the following scheme:



wherein P^3 represents a suitable protecting group such as Boc.

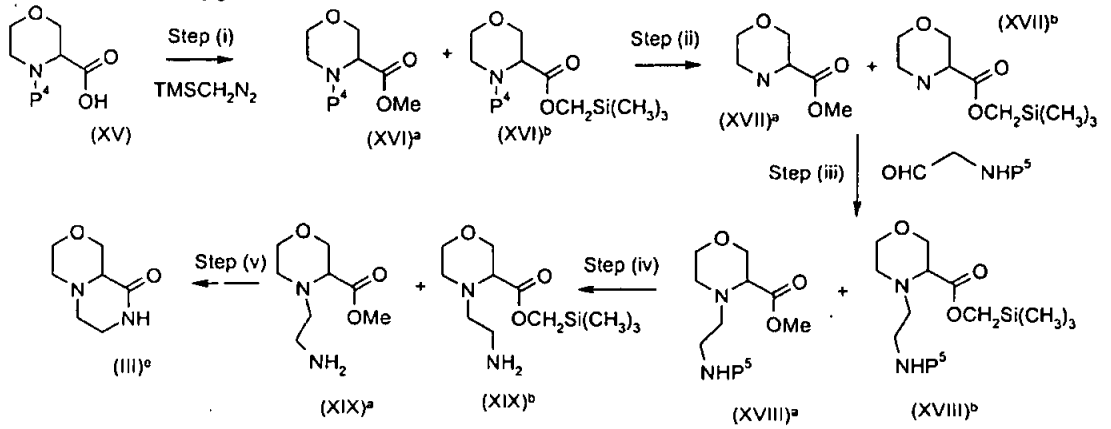
Step (i) typically comprises reaction with 1,1-dimethylethyl (2-oxoethyl)carbamate in the presence of sodium triacetoxyborohydride in a suitable solvent such as 1,2-dichloroethane.

Step (ii) typically comprises a deprotection reaction, for example, when P^3 represents Boc, said deprotection reaction may typically comprise reacting a compound of formula (XII) with trifluoroacetic acid in dichloromethane, and then purifying the product on a SCX (Strong Cationic Exchange) silica cartridge.

Step (iii) typically comprises heating the previous deprotected intermediate in a suitable solvent such as acetonitrile at a suitable temperature, such as 60°C.

Step (iv) typically comprises the use of borane tetrahydrofuran complex solution at a suitable temperature, such as 0°C, followed by treatment with an aqueous acid, such as hydrochloric acid, and purification on a SCX (Strong Cationic Exchange) silica cartridge.

Compounds of formula (III) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents =O, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents an oxygen atom may be prepared in accordance with the following scheme:



wherein P^4 and P^5 represent a suitable protecting group such as Boc.

Step (i) typically comprises reacting a compound of formula (XV) with a trimethylsilyl diazomethane solution at room temperature.

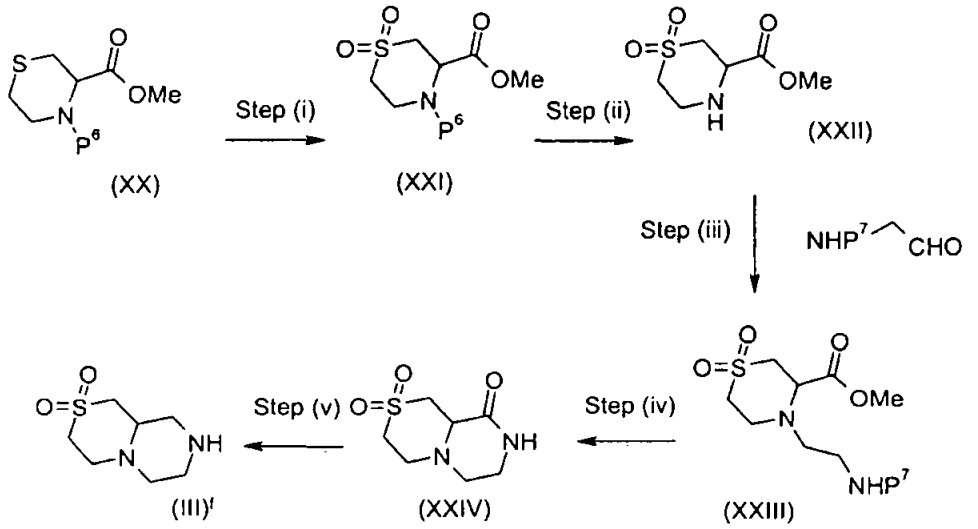
Step (ii) typically comprises a deprotection reaction, for example, when P^4 represents Boc, said deprotection reaction may typically comprise reacting the compounds of formulae $(XVI)^a$ and $(XVI)^b$ with trifluoroacetic acid in dichloromethane.

Step (iii) typically comprises reacting the compounds of formulae $(XVII)^a$ and $(XVII)^b$ with N-boc-2-aminoacetaldehyde in the presence of sodium triacetoxyborohydride in a suitable solvent such as 1,2-dichloroethane.

Step (iv) typically comprises a deprotection reaction, for example, when P^5 represents Boc, said deprotection reaction may typically comprise reacting the compounds of formulae $(XVIII)^a$ and $(XVIII)^b$ with trifluoroacetic acid in dichloromethane, followed by purification on a SCX (Strong Cationic Exchange) silica cartridge.

Step (v) typically comprises heating at a suitable temperature such as 40°C the compounds of formulae $(XIX)^a$ and $(XIX)^b$ in a suitable solvent such as methanol.

Compounds of formula (III) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents $-S(O_2)-$ may be prepared in accordance with the following scheme:



wherein P^6 and P^7 represent a suitable protecting group such as Boc.

Step (i) typically comprises reacting a compound of formula (XX) with MCPBA (3-chloroperbenzoic acid) in dichloromethane.

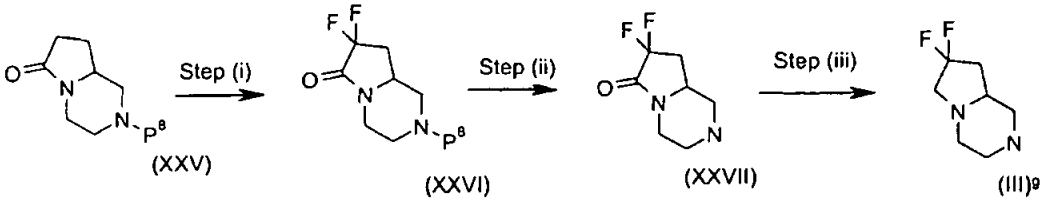
Step (ii) typically comprises a deprotection reaction, for example, when P^6 represents Boc, said deprotection reaction may typically comprise reacting the compound of formula (XXI) with trifluoroacetic acid in dichloromethane.

Step (iii) typically comprises reacting a compound of formula (XXII) with N-boc-2-aminoacetaldehyde in the presence of sodium triacetoxyborohydride in a suitable solvent such as 1,2-dichloroethane.

Step (iv) typically comprises a deprotection reaction, for example, when P^7 represents Boc, said deprotection reaction may typically comprise reacting the compound of formula (XXIII) with trifluoroacetic acid in dichloromethane followed by purification on a SCX (Strong Cationic Exchange) silica cartridge.

Step (v) typically comprises reacting a compound of formula (XXIV) with borane tetrahydrofuran complex solution at a suitable temperature, such as 50°C, followed by treatment with an aqueous acid, such as hydrochloric acid, and purification on a SCX (Strong Cationic Exchange) silica cartridge.

Compounds of formula (III) wherein p and q both represent 1, n represents 0, X represents a nitrogen atom, Y represents $-C(H_2)-$, Z represents $-C(H_2)-$, m represents 2 and both R^1 groups represent fluorine may be prepared in accordance with the following scheme:



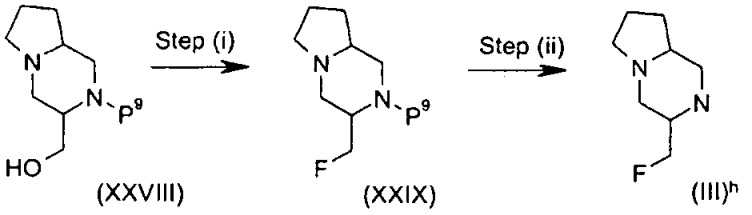
wherein P^8 represents a suitable protecting group such as t-butoxycarbonyl.

Step (i) typically comprises reaction with a suitable base such as lithium bis(dimethylethylsilyl)amide in a suitable solvent such as THF at a suitable temperature such as -78°C, followed by a suitable fluorinating agent such as *N*-fluorobenzenesulfonimide.

Step (ii) typically comprises a deprotection reaction, for example, when P^8 represents t-butoxy carbonyl said deprotection reaction may typically comprise reacting a compound of formula (XXVI) with a mixture of dichloromethane and trifluoroacetic acid, followed by purification on a SCX (Strong Cationic Exchange) silica cartridge.

Step (iii) typically comprises reacting a compound of formula (XXVII) with borane tetrahydrofuran complex solution at a suitable temperature, such as 50°C, followed by treatment with an aqueous acid, such as hydrochloric acid, and purification on a SCX (Strong Cationic Exchange) silica cartridge.

Compounds of formula (III) wherein p and q both represent 1, m represents 0, X represents a nitrogen atom, Y and Z both represent $-C(H_2)-$, n represents 1 and R^2 represents haloC_{1-6} alkyl (e.g. fluoroethyl) may be prepared in accordance with the following scheme:

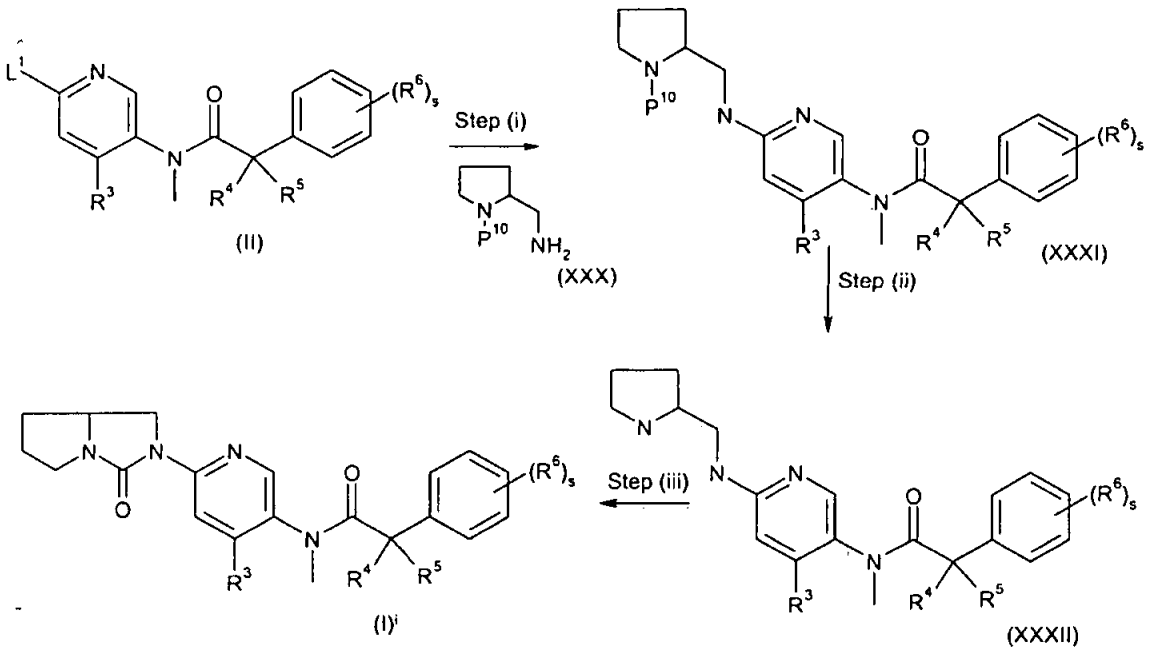


wherein P^9 represents a suitable protecting group such as benzyl.

Step (i) typically comprises reaction with a fluorinating agent such as DAST ((diethylamino)sulfur trifluoride) in a suitable solvent such as dichloromethane at a suitable temperature such as room temperature.

Step (ii) typically comprises a deprotection reaction, for example, when P^9 represents benzyl said deprotection reaction may typically comprise reacting a compound of formula (XXIX) with hydrogen in the presence of a suitable catalyst such as palladium on carbon, followed by purification on a SCX (Strong Cationic Exchange) silica cartridge.

Compounds of formula (I) wherein p represents 0, q represents 1, m represents 0, n represent 1, R^2 represents =O, X represents a nitrogen atom and Y and Z both represent -$C(H_2)$-, may be prepared in accordance with the following scheme:



wherein L^1, R^3, R^4, R^5, R^6 and s are as defined above and P^{10} represents a suitable leaving group such as Boc.

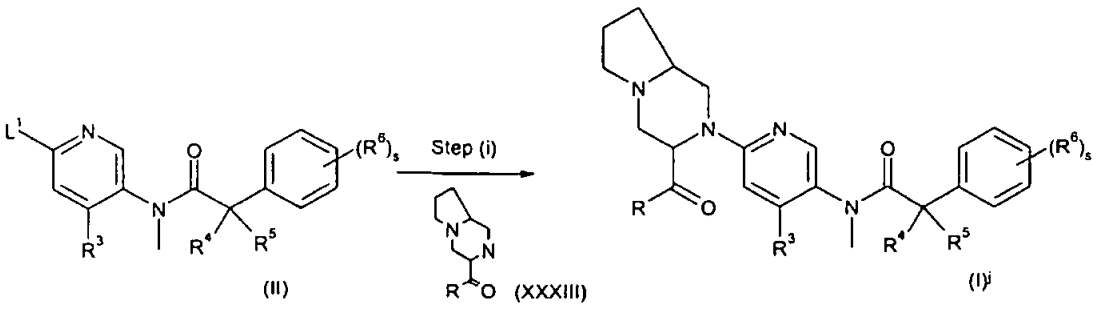
Step (i) typically comprises reaction with 1,1-dimethylethyl 2-(aminomethyl)-1-pyrrolidinecarboxylate in a suitable solvent such as DMSO in the presence of a suitable base such as potassium carbonate at a suitable temperature such as 180°C under microwave irradiation.

Step (ii) typically comprises a deprotection reaction, for example, when P^{10} represents Boc said deprotection reaction may typically comprise reacting a compound of formula (-) with a mixture of dichloromethane and trifluoroacetic acid, followed by purification on a SCX (Strong Cationic Exchange) silica cartridge

Step (iii) typically comprises reacting a compound of formula (XXXI) with triphosgene in the presence of a suitable base such as triethylamine at a suitable temperature such as room temperature.

Compounds of formula (I) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents $-CONH_2$, CO_2H or CO_2Et, X represents a nitrogen atom and Y and Z both represent -$C(H_2)$- may be prepared in accordance with the following scheme:

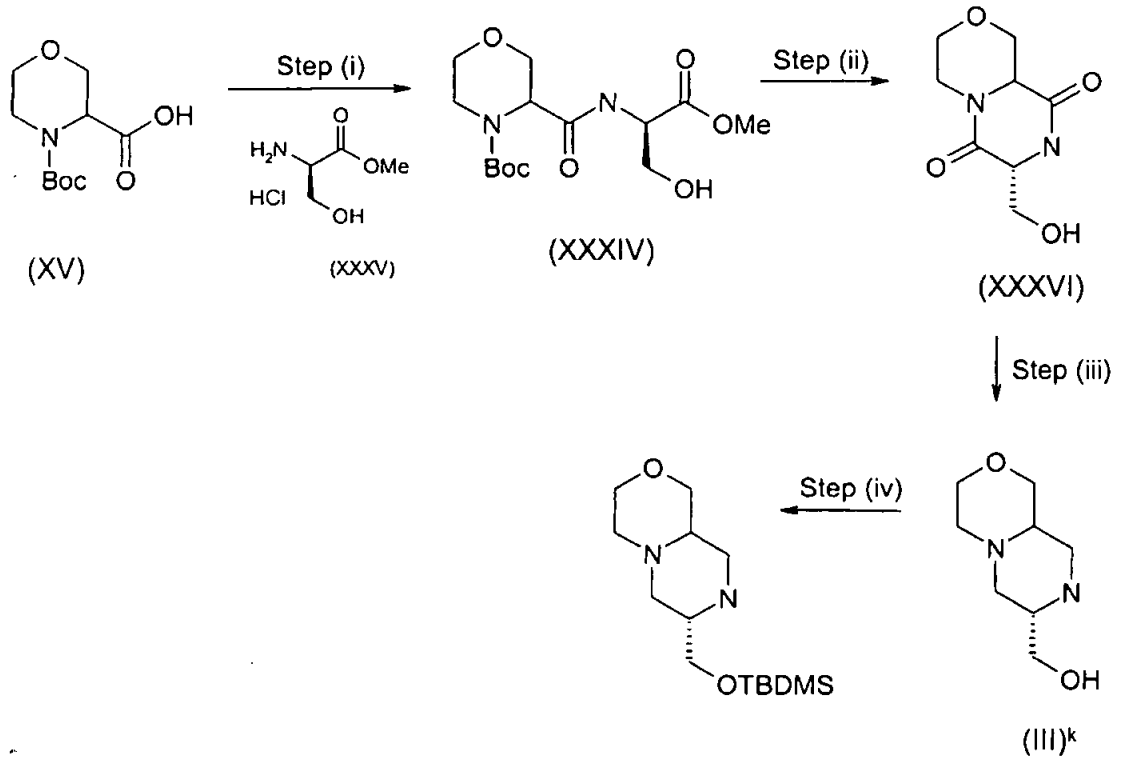
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wherein L^1, R^3, R^4, R^5, R^6 and s are as defined above and R represents NH_2, OH or OEt.

Step (i) typically comprises reaction with octahydropyrrolo[1,2-*a*]pyrazine-3-carboxylic acid, amide or ester in a suitable in the presence of a suitable base such as triethylamine at a suitable temperature such as 150°C.

Compounds of formula (III) wherein p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents an oxygen atom, m represents 0, n represents 1 and R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, protected as the TBDMS derivative, may be prepared according to the following scheme:



Step (i) typically comprises reaction of the carboxylic acid (XV) with the amine of formula (XXXV) in a suitable solvent, such as dichloromethane, in the presence of a suitable coupling reagent such as *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) and a suitable base, such as diisopropylethylamine at a suitable temperature, such as room temperature.

Step (ii) typically comprises deprotection of (XXXIV) using a suitable reagent such as trifluoroacetic acid, followed by purification on a SCX (Strong Cationic Exchange) silica cartridge and subsequent cyclisation at a suitable temperature, such as 50°C.

Step (iii) typically comprises reduction of (XXXVI) using a suitable reducing agent such as BH_3-THF at a suitable temperature such as reflux.

Step (iv) typically comprises reaction of $(III)^k$ with *tert*-butyldimethylsilyl chloride (TBDMSCl) in a suitable solvent , such as dichloromethane, in the presence of a suitable base, such as triethylamine at a suitable temperature, such as room temperature.

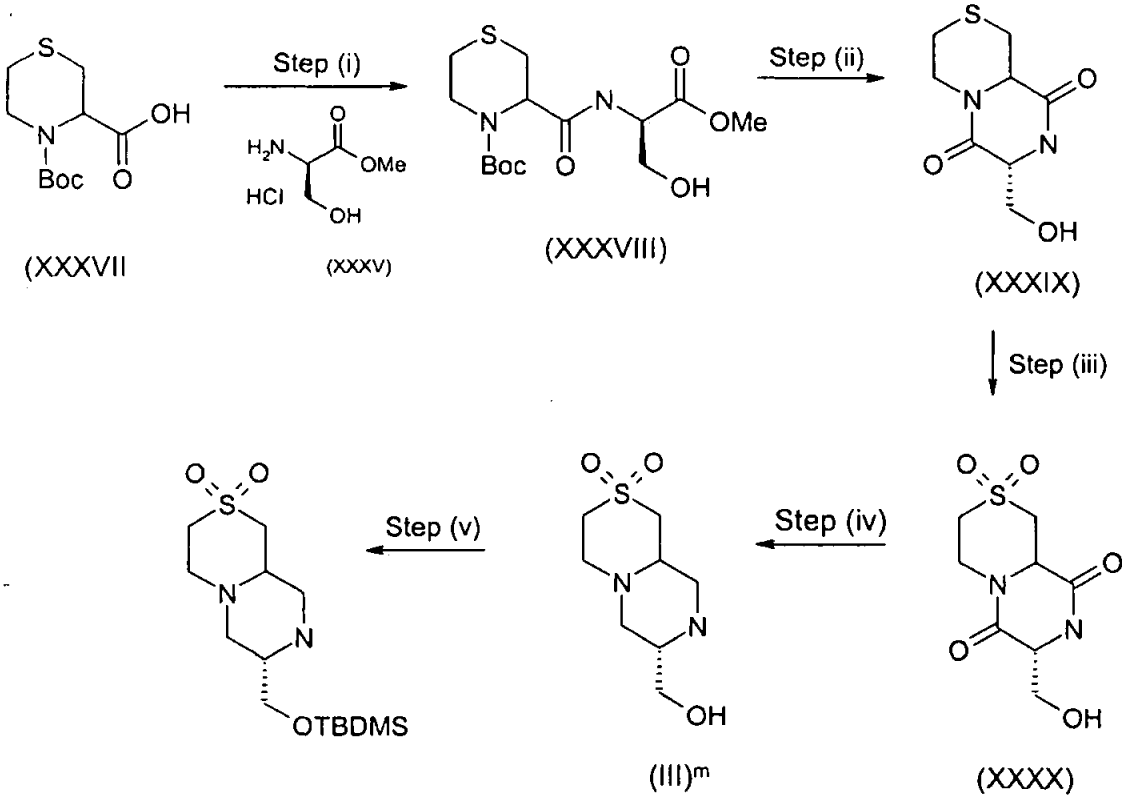
Compounds of formula (III) wherein p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents an oxygen atom, m represents 0, n represents 1 and R^2 represents C_{1-6} alkyl may be prepared in an analogous manner to that described above, starting from the appropriate amine in place of that of formula (XXXV) above.

Compounds of formula (III) wherein p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents $-N(R^z)-$, m represents 0, n represents 1 and R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, protected as the TBDMS derivative, may be prepared in an analogous manner to that described above when Z represents an oxygen atom, starting from the corresponding carboxylic acid wherein Z represents $N\text{-}P^{11}$ and P^{11} represents a suitable protecting group such as Boc. Compounds of formula (III) wherein R^z is C_{1-6} alkyl, C_{1-6} alkoxy, $-COR^7$ or $-SO_2R^7$ may be derived from compounds of formula (III) when R^z is hydrogen at any suitable point in the synthetic sequence, for example after step (iv), *via* deprotonation employing a suitable base such as triethylamine followed by reaction of the resultant anion with $R^z\text{-}L^2$, wherein L^2 is a suitable leaving group such as halogen, under standard conditions, described in many standard organic chemistry texts, such as 'March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure' by Michael B. Smith and Jerry March, fifth edition (Wiley, 2001), incorporated herein by reference.

Compounds of formula (III) wherein p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents $-N(R^z)-$, m represents 0, n represents 1 and R^2 represents C_{1-6} alkyl, may be prepared in an analogous manner to that described above when Z represents an oxygen atom, starting from the corresponding carboxylic acid, wherein Z represents $N\text{-}P^{11}$ and P^{11} represents a suitable protecting group such as Boc,

and the appropriate amine in place of that of formula (XXXV) above. Compounds of formula (III) wherein R^z is C_{1-6} alkyl, C_{1-6} alkoxy, $-COR^7$ or $-SO_2R^7$ may be derived from compounds of formula (III) when R^z is hydrogen at any suitable point in the synthetic sequence *via* deprotonation employing a suitable base such as triethylamine followed by reaction of the resultant anion with R^z-L^2, wherein L^2 is a suitable leaving group such as halogen, under standard conditions, described in many standard organic chemistry texts, such as 'March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure' by Michael B. Smith and Jerry March, fifth edition (Wiley, 2001), incorporated herein by reference.

Compounds of formula (III) wherein p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents $-S(O_2)-$, n represents 1 and R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, protected as the TBDMS derivative, may be prepared according to the following scheme:



(XXXVII) (XXXV) (XXXVIII) (XXXIX) (XXXX) $(III)^m$

Step (i) typically comprises reaction of the carboxylic acid (XXXVII) with the amine of formula (XXXV) in a suitable solvent, such as dichloromethane, in the presence of a suitable coupling reagent such as *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) and a suitable base, such as diisopropylethylamine at a suitable temperature, such as room temperature.

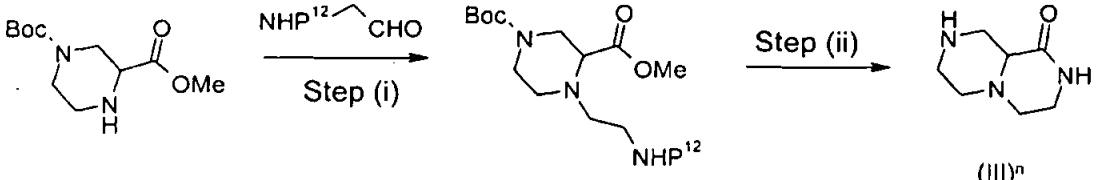
Step (ii) typically comprises deprotection of (XXXVIII) using a suitable reagent such as trifluoroacetic acid, followed by purification on a SCX (Strong Cationic Exchange) silica cartridge and subsequent cyclisation under suitable conditions, such as microwave irradiation.

Step (iii) typically comprises oxidation of (XXXIX) employing a suitable oxidising agent such as 3-chloroperoxybenzoic acid (m-CPBA), in a suitable solvent such as dichloromethane, at a suitable temperature, such as room temperature.

Step (iv) typically comprises reduction of (XXXX) using a suitable reducing agent such as BH_3-THF at a suitable temperature such as reflux.

Step (v) typically comprises reaction of $(III)^m$ with *tert*-butyldimethylsilyl chloride (TBDMSCl) in a suitable solvent , such as dichlorormethane, in the presence of a suitable base, such as triethylamine at a suitable temperature, such as room temperature.

Compounds of formula (III) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents =O, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents NH may be prepared in accordance with the following scheme:



(XXXXI) (XXXXII) $(III)^n$

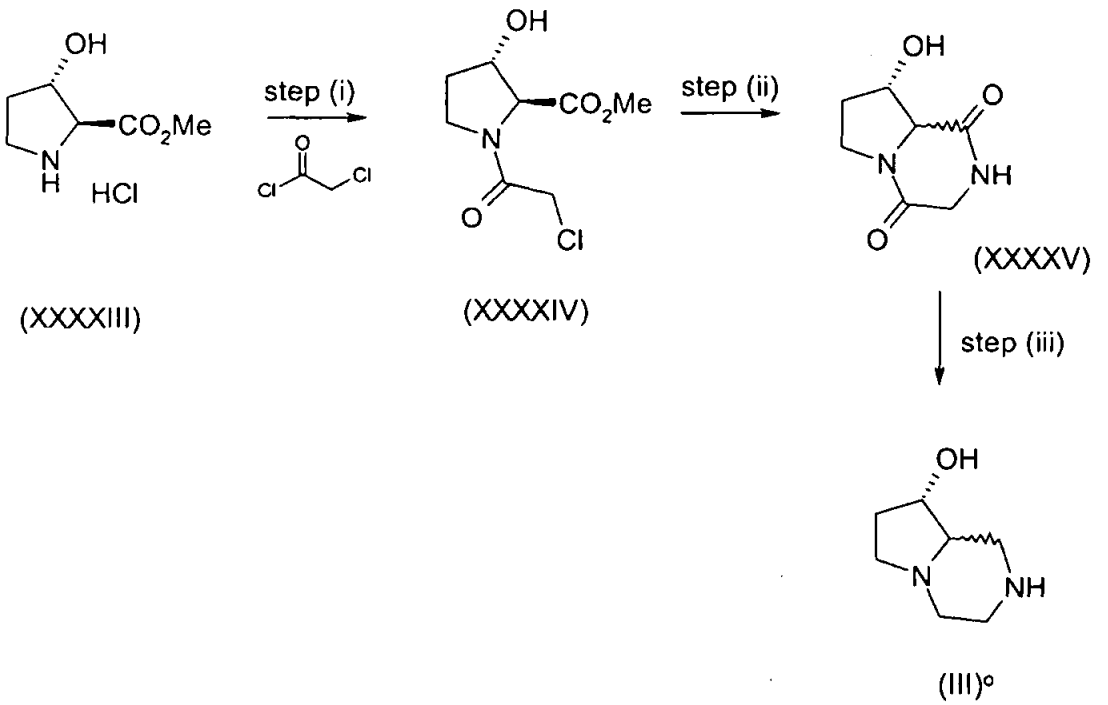
wherein P^{12} represents a suitable protecting group such as Boc.

Step (i) typically comprises reacting a compound of formula (XXXXI) with N-boc-2-aminoacetaldehyde in the presence of sodium triacetoxyborohydride in a suitable solvent such as 1,2-dichloroethane.

Step (ii) typically comprises a deprotection reaction, for example, when P^{12} represents Boc, said deprotection reaction may typically comprise reacting the compound of formula (XXXXII) with trifluoroacetic acid in dichloromethane followed by purification on a SCX (Strong Cationic Exchange) silica cartridge, followed by cyclization.

Compounds of formula (III) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$ and Z represents NH may be prepared from compounds of formula $(III)^n$ *via* reduction with a suitable reducing agent such as borane-THF, at elevated temperature, such as 75°C, in a suitable solvent, such as THF.

Compounds of formula (III) wherein p and q both represent 1, m represents 1, n represents 0, R^1 represents hydroxyl, X represents a nitrogen atom, Y represents -C(H_2) and Z represents -C(H_2) may be prepared in accordance with the following scheme:



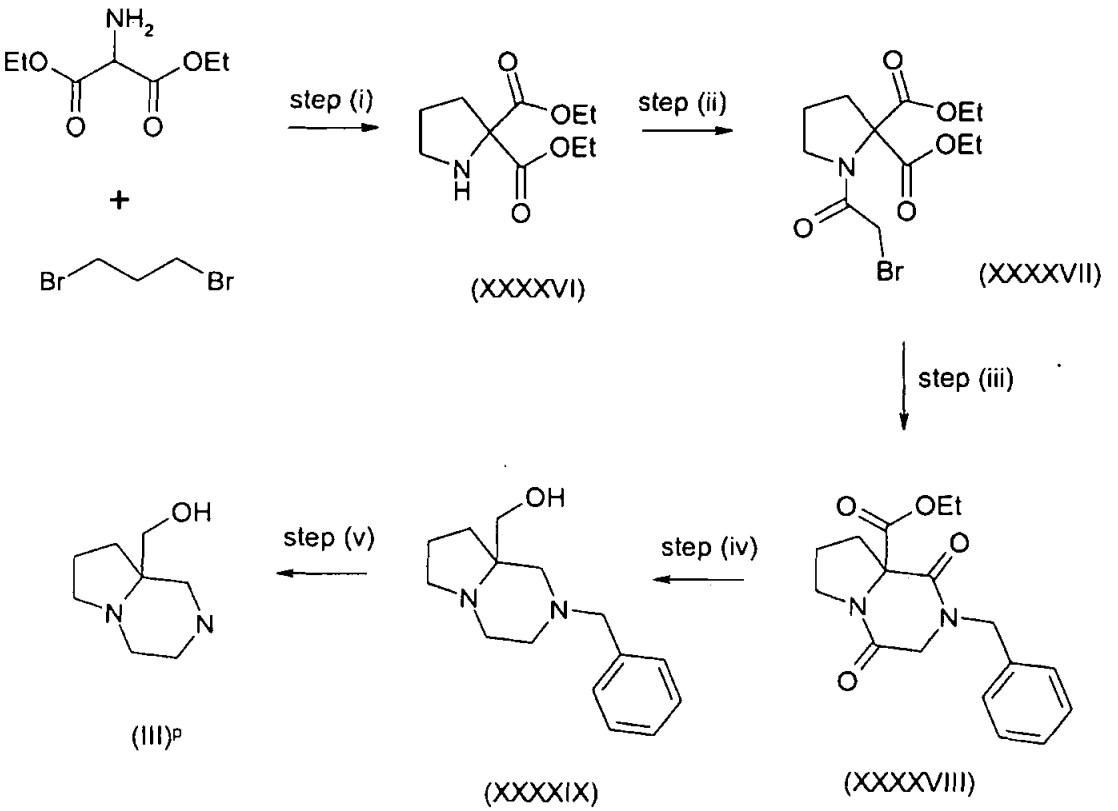
(XXXXIII) (XXXXIV) (III)°

Step (i) typically comprises reacting a compound of formula (XXXXIII) with chloroacetyl chloride in the presence of a suitable base, such as triethylamine.

Step (ii) typically comprises treating (XXXXIV) with methanolic ammonia at room temperature.

Step (iii) typically comprises reduction of the diketopiperazine of formula (XXXXV) with a suitable reducing agent, such as $LiAlH_4$, in a suitable solvent, such as THF, at room temperature.

Compounds of formula (III) wherein p and q both represent 1, m and n both represent 0, X represents a nitrogen atom, Y represents -C(H_2), Z represents -C(H_2) and A represents CH_2OH may be prepared in accordance with the following scheme:



Typically compounds of formula (XXXXVI) may be prepared by reacting diethyl aminomalonate with 1,3-dibromopropane in the presence of sodium ethoxide, in a suitable solvent such as ethanol, at a suitable elevated temperature, such as reflux (step (i)).

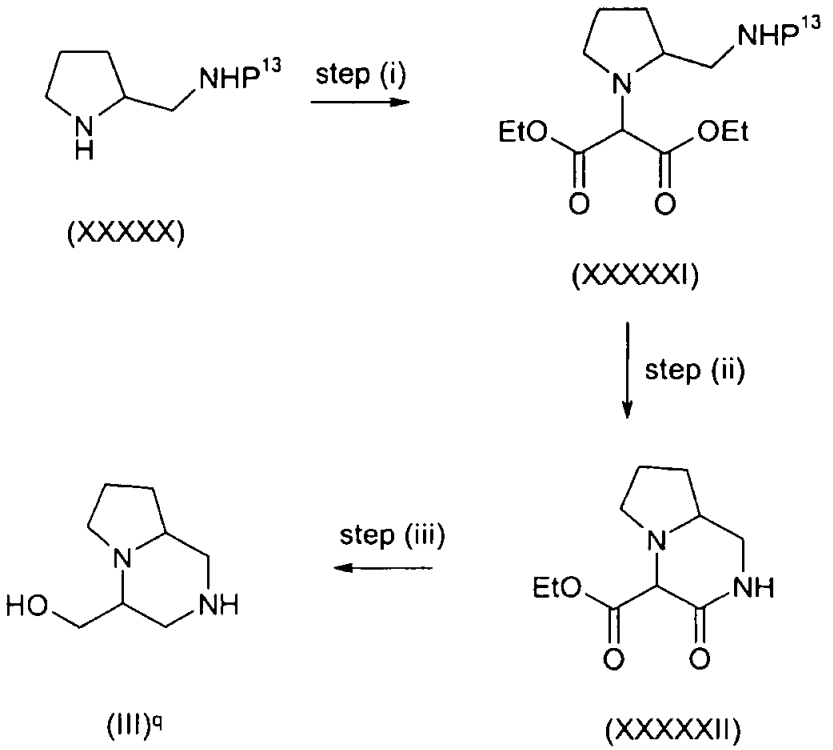
Typically step (ii) may be performed *via* reaction of (XXXXVI) with bromoacetyl bromide in the presence of a suitable base, such as potassium carbonate at 0°C.

Typically step (iii) involves treatment of (XXXXVII) with benzylamine in a suitable solvent, such as acetonitrile, at room temperature.

Typically step (iv) involves reduction of (XXXXVIII) using a suitable reducing agent such as $LiAlH_4$, in a suitable solvent such as THF at elevated temperature, such as reflux.

Typically step (v) involves deprotection under standard conditions, such as treating with ammonium formate and palladium on carbon, in a suitable solvent such as methanol, at an elevated temperature, such as reflux.

Compounds of formula (III) wherein p and q both represent 1, m represents 0, n represents 1, R^2 represents CH_2OH, X represents a nitrogen atom, Y represents $-C(H_2)$, Z represents $-C(H_2)$ may be prepared in accordance with the following scheme:



wherein P^{13} represents a suitable protecting group such as benzyloxycarbonyl.

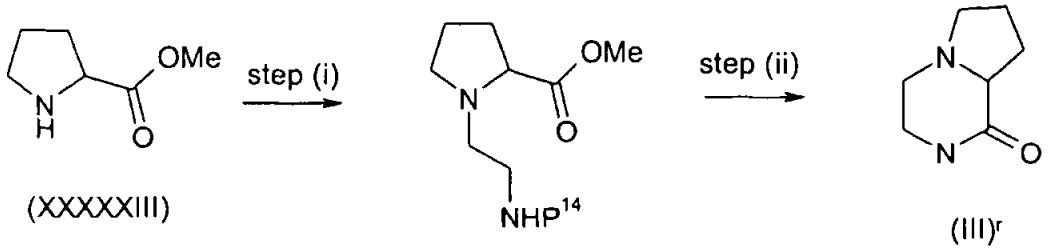
Typically step (i) may be performed by reaction of a compound of formula (XXXXX) with diethylbromomalonate in the presence of a base, such as potassium carbonate, in a suitable solvent, such as acetonitrile at room temperature.

Typically step (ii) may be performed *via* deprotection of compound (XXXXXI) under standard conditions, such as under an atmosphere of hydrogen in the presence of palladium on carbon, followed by cyclization at an elevated temperature, such as 50°C.

Typically step (iii) may be performed *via* reduction of the ester moiety of (XXXXXII) employing a suitable reducing agent, such as $LiBH_4$ in a solvent such as THF, followed by reduction of the amide carbonyl moiety employing a suitable reagent, such as BH_3-THF, at elevated temperature, such as reflux.

Compounds of formula (III) wherein p and q both represent 1, X represents nitrogen, Y represents $-(C(H_2)-)_2$, Z represents an oxygen atom, m represents 0, n represents 1 and R^2 represents haloC_{1-6} alkyl may be prepared from compounds of formula $(III)^k$ *via* protection of the secondary NH, for example using a benzyl group, followed by conversion of the hydroxyalkyl moiety to a haloC_{1-6} alkyl moiety *via* treatment with a halogenating agent such as DAST [(diethylamino)sulphur trifluoride], followed by deprotection under standard conditions.

Compounds of formula (III) wherein p represents 1, q represents 1, m represents 0, n represents 1, R^2 represents =O, X represents a nitrogen atom, Y represents -C(H_2)- and Z represents -C(H_2)- may be prepared in accordance with the following scheme:



(XXXXXIII) (XXXXXIV) $(III)^r$

wherein P^{14} represents a suitable protecting group such as Boc.

Typically step (i) may be performed *via* reaction of (XXXXXIII) with 1,1-dimethylethyl (2-oxoethyl)carbamate in the presence of sodium triacetoxyborohydride in a suitable solvent such as 1,2-dichloroethane.

Step (ii) typically comprises a deprotection reaction, for example, when P represents Boc, said deprotection reaction may typically comprise reacting a compound of formula (XXXXXIV) with trifluoroacetic acid in dichloromethane, and then purifying the product on a SCX (Strong Cationic Exchange) silica cartridge. The deprotected intermediate may then be cyclized *via* heating at a suitable temperature, such as 40°C

Compounds of formula (IV), (VII), (IX), (XI), (XV), (XX), (XXV), (XXVIII), (XXX), (XXXIII), (XXXV), (XXXVII),(XXXXI), (XXXXIII), (XXXXX) and (XXXXXIII) are either known or may be prepared in accordance with known procedures.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists of the NK1 and NK3 receptor and thus may be of use in the treatment of psychotic disorders.

Within the context of the present invention, the terms describing the indications used herein are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

Within the context of the present invention, the term "psychotic disorder" includes :-

Schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

Compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may also be of use in the treatment of the following disorders:-

Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90):

Anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00):

Substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-

Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89),

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Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide:

Sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; sleep apnea and jet-lag syndrome:

Eating disorders such as Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; Binge Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50):

Autism Spectrum Disorders including Autistic Disorder (299.00), Asperger's Disorder (299.80), Rett's Disorder (299.80), Childhood Disintegrative Disorder (299.10) and Pervasive Disorder Not Otherwise Specified (299.80, including Atypical Autism).

Attention-Deficit/Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder

Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23):

Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301,22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301,83), Histrionic Personality Disorder (301.50), Narcissistic Personality Disorder (301,81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9):

Enhancement of cognition including the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease: and

Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

All of the various forms and sub-forms of the disorders mentioned herein are contemplated as part of the present invention.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above psychotic disorders, in particular schizophrenia.

The invention further provides a method of treating schizophrenia which comprises administering to a host in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of schizophrenia.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of the invention may be used in combination with the following agents to treat or prevent psychotic disorders: i) antipsychotics; ii) drugs for extrapyramidal side effects, for example anticholinergics (such as benztropine, biperiden, procyclidine and trihexyphenidyl), antihistamines (such as diphenhydramine) and dopaminergics (such as amantadine); iii) antidepressants; iv) anxiolytics; and v) cognitive enhancers for example cholinesterase inhibitors (such as tacrine, donepezil, rivastigmine and galantamine).

The compounds of the invention may be used in combination with antidepressants to treat or prevent depression and mood disorders.

The compounds of the invention may be used in combination with the following agents to treat or prevent bipolar disease: i) mood stabilisers; ii) antipsychotics; and iii) antidepressants.

The compounds of the invention may be used in combination with the following agents to treat or prevent anxiety disorders: i) anxiolytics; and ii) antidepressants.

The compounds of the invention may be used in combination with the following agents to improve nicotine withdrawal and reduce nicotine craving: i) nicotine replacement therapy for example a sublingual formulation of nicotine beta-cyclodextrin and nicotine patches; and ii) bupropion.

The compounds of the invention may be used in combination with the following agents to improve alcohol withdrawal and reduce alcohol craving: i) NMDA receptor antagonists for example acamprosate; ii) GABA receptor agonists for example tetrabamate; and iii) Opioid receptor antagonists for example naltrexone.

The compounds of the invention may be used in combination with the following agents to improve opiate withdrawal and reduce opiate craving: i) opioid mu receptor agonist/opioid kappa receptor antagonist for example buprenorphine; ii) opioid receptor antagonists for example naltrexone; and iii) vasodilatory antihypertensives for example lofexidine.

The compounds of the invention may be used in combination with the following agents to treat or prevent sleeping disorders: i) benzodiazepines for example temazepam, lormetazepam, estazolam and triazolam; ii) non-benzodiazepine hypnotics for example zolpidem, zopiclone, zaleplon and indiplon; iii) barbiturates for example aprobarbital, butabarbital, pentobarbital, secobarbita and phenobarbital; iv) antidepressants; v) other sedative-hypnotics for example chloral hydrate and chlormethiazole.

The compounds of the invention may be used in combination with the following agents to treat anorexia: i) appetite stimulants for example cyproheptidine; ii) antidepressants; iii) antipsychotics; iv) zinc; and v) premenstral agents for example pyridoxine and progesterones.

The compounds of the invention may be used in combination with the following agents to treat or prevent bulimia: i) antidepressants; ii) opioid receptor antagonists; iii) antiemetics for example ondansetron; iv) testosterone receptor antagonists for example flutamide; v) mood stabilisers; vi) zinc; and vii) premenstral agents.

The compounds of the invention may be used in combination with the following agents to treat or prevent autism: i) antipsychotics; ii) antidepressants; iii) anxiolytics; and iv) stimulants for example methylphenidate, amphetamine formulations and pemoline.

The compounds of the invention may be used in combination with the following agents to treat or prevent ADHD: i) stimulants for example methylphenidate, amphetamine formulations and pemoline; and ii) non-stimulants for example norepinephrine reuptake

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.

When a compound of formula (I) 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.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration.

The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions suitable for transdermal administration include ointments, gels and patches.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

Experimental

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Proton Magnetic Resonance (NMR) spectra were recorded on Varian instruments at 300, 400 or 500 MHz, on Bruker instrument at 300 MHz, chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. The NMR spectra were recorded at temperature ranging from 25 to 90°C; when more than one conformer was detected the chemical shifts for the most abundant one is reported. Mass spectra (MS) were taken on a 4 II triple quadrupole Mass Spectrometer (Micromass UK) or on a Agilent MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode or on a Agilent LC/MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode coupled with HPLC instrument Agilent 1100 Series [LC/MS - ES (+):analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3µm) (mobile phase: 100% [water +0.1% HCO_2H] for 1 min, then from 100% [water +0.1% HCO_2H] to 5% [water +0.1% HCO_2H] and 95% [CH_3CN] in 5 min, finally under these conditions for 2 min; T=40°C; flux= 1 ml/min; LC/MS - ES (-):analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3µm) (mobile phase: 100% [water +0.05% NH_3] for 1 min, then from 100% [water +0.05% NH_3 to 5% [water +0.05% NH_3] and 95% [CH_3CN] in 5 min, finally under these conditions for 2 min; T=40°C; flux= 1 ml/min]. In the mass spectra only one peak in the molecular ion cluster is reported. Optical rotations were determined at 20°C with a Jasco DIP360 instrument (l=10 cm, cell volume = 1 ml, λ = 589 nm) unless otherwise stated. Flash silica gel chromatography was carried out over silica gel 230-400 mesh supplied by Merck AG Darmstadt, Germany or over Varian Mega Be-Si pre-packed cartridges or over pre-packed Biotage silica cartridges.

HPLC (walk –up) refers to HPLC analysis performed on a Luna C18 (mobile phase: from 100% [water +0.05%TFA] to 5% [water +0.05%TFA] and 95% [CH_3CN +TFA 0.05%] in 8 min; T=40°C; flux= 1 ml/min).

UPLC refers to UPLC analysis performed on a UPLC Waters Acquity System. UPLC/MS refers to UPLC analysis performed on a UPLC Waters Acquity System coupled with an MS-Detector Waters ZQ (single quad.), ms range 100-1000. UPLC mobile phase data:

Gradient before sample organiser

A = H_2O + 0.1% formic acid
B= MeCN + 0.075% formic acid

Time(min)	Flow rate (mL/min)	%A	%B	curve
1. Initial	1.000	97.0	3.0	init
2. 0.10	1.000	94.0	6.0	6
3. 0.60	1.000	30.0	70.0	6
4. 1.10	1.000	1.0	99.0	6
5. 1.45	1.000	97.0	3.0	11

Gradient after sample organiser (adjusted to give same retention times as those achieved prior to installation of the sample organiser)

Time(min)	Flow Rate	%A	%B	Curve
1. Initial	1.000	97.0	3.0	Initial
2. 0.05	1.000	94.0	6.0	6
3. 0.57	1.000	30.0	70.0	6
4. 1.06	1.000	1.0	99.0	6
5. 1.45	1.000	97.0	3.0	11

curve 6 = linear gradient
curve 11 = change at the end

Waters Acquity 2996 PDA

Start Wavelength (nm)	210.00
End Wavelength (nm)	350.00
Resolution (nm)	2.4
Sampling Rate (spectra/s)	20.000
Filter Response	0
Exposure Time(ms)	Automatic

Interpolate 656	Yes
Acquisition stop time (mins)	1.50

T.l.c. refers to thin layer chromatography on 0.25 mm silica gel plates (60F-254 Merck) and visualized with UV light. For phase separations performed by using microfiltration devices: phase separation cartridge with polypropylene frit by Whatman or Alltech. SCX means: SCX-cartridges (loading 0.75mmol\g) by Varian.

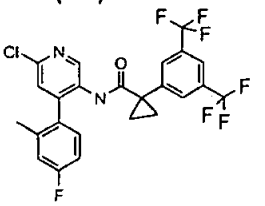
Solutions were dried over anhydrous sodium sulphate.

The following abbreviations are used in the text: AcOEt = ethyl acetate, CH = cyclohexane, DCM = methylene chloride, DIPEA = N,N-diisopropylethylamine, DMF = N,N'-dimethylformamide, Et_2O = diethyl ether, EtOH = ethanol, MeOH = methanol, TEA = triethylamine, THF = tetrahydrofuran, TFA = trifluoroacetic acid, CH_3CN= acetonitrile, std = saturated.

* indicates a stereocentre of fixed but unknown stereochemistry i.e. either *R* or *S* stereochemistry.
Diastereoisomer 1 or Diastereoisomer 2 means a compound of the invention or an intermediate thereof as a single diastereoisomer whose absolute configuration at one stereocentre was not determined.

Enantiomer 1 or Enantiomer 2 means a compound of the invention or an intermediate thereof as a single enantiomer whose absolute configuration was not determined.

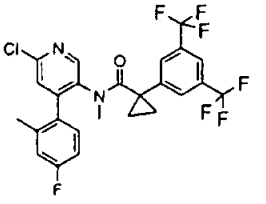
Description 1
1-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]cyclopropanecarboxamide (D1)



1-[3,5-Bis(trifluoromethyl)phenyl]cyclopropanecarboxylic acid (400 mg, 1.34 mmol) was dissolved in dichloromethane (6 ml), oxalyl chloride (0.24 ml, 2.68 mmol) was added, followed by dimethylformamide (5 µl, cat.). The solution was stirred for 3 hrs. The solution was concentrated under vacuum. The crude was dissolved in toluene, 6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinamine (380 mg, 1.61 mmol) was added, followed by diisopropylethylamine (0.7 ml, 4 mmol) and dimethylaminopyridine (164 mg, 1.34 mmol), and the solution was warmed at 100 °C overnight. The solution was added to ethyl acetate, washed with saturated aqueous NH_4Cl and brine and concentrated under vacuum. The

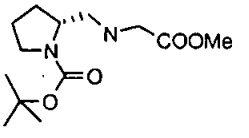
product was isolated by chromatography (silica, cyclohexane/EtOAc 90/10 – 80/20) as a white solid: 635 mg, 1.23 mmol, 92% yield.
MS (ES/+): m/z = 517 $[M+H]^+$.
NMR ($CDCl_3$): δ (ppm): 9.61 (s, 1H); 7.79 (s, 1H); 7.68 (s, 2H); 7.01 (s, 1H); 6.81-6.68 (m, 3H); 6.43 (s, 1H); 1.88 (s, 3H); 1.60 (s, 4H)
Rf: 0.35 (cyclohexane/EtOAc 80/20)

Description 2
1-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]cyclopropanecarboxamide (D2)



1-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]cyclopropanecarboxamide (D1; 310 mg, 0.6 mmol) was dissolved in dimethylformamide (6 ml). Methyl iodide (51.6 µl, 1.2 mmol) was added, followed by cesium carbonate (393 mg, 1.2 mmol), and the suspension was stirred overnight). The suspension was partitioned between ethyl acetate and saturated aqueous NH_4Cl, and the organic phase was washed with brine and concentrated under vacuum. The product was isolated by chromatography (silica, cyclohexane/EtOAc 90/10 – 80/20) as a white solid: 300 mg, 0.56 mmol, 93% yield.
MS (ES/+): m/z = 531 $[M+H]^+$.
NMR (DMSO-d_6): δ (ppm) 8.34 (s, 1H); 7.88 (s, 1H); 7.70 (s, 2H); 7.40 (s, 1H); 7.06 (dd, 1H), 6.90 (m, 2H); 2.97 (s, 3H), 2.11 (s,3H), 1.21-1.37 (m, 4H)
Rf: 0.3 (cyclohexane/EtOAc 80/20)

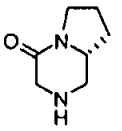
Description 3
1,1-Dimethylethyl (2*R*)-2-({[2-(methyloxy)-2-oxoethyl]amino}methyl)-1-pyrrolidinecarboxylate (D3)



1,1-Dimethylethyl (2*R*)-2-formyl-1-pyrrolidinecarboxylate (1. g, 5.02 mmol) was dissolved in 20 ml of anhydrous dichloroethane. Methyl glycinate hydrochloride (0.95 g, 7.57 mmol) was added, followed after 30 min by sodium triacetoxyborohydride (2.2 g, 10.38 mmol). The reaction was stirred for 8hrs at room temperature. The reaction mixture was diluted with methanol to obtain a clear solution, which was passed through a SCX cartridge. The product was eluted with 1 M methanolic ammonia. The product was isolated by

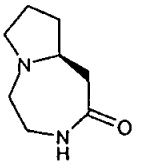
chromatography (silica, dichloromethane/methanol 95/5) as colourless oil: 800 mg, 2.94 mmol.
MS (ES/+): m/z = 273 $[M+H]^+$.
NMR ($CDCl_3$): δ (ppm): 4.01 (bs, 1H); 3.75 (s, 3H); 3.53-3.30 (m, 4H); 2.94-2.53 (m, 3H); 1.92-1.76 (m, 3H); 1.48 (s, 9H).
Rf: 0.40 (cyclohexane/EtOAc 1/1)

Description 4
(8a*R*)-Hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one (D4)



1',1-Dimethylethyl (2*R*)-2-({[2-(methyloxy)-2-oxoethyl]amino}methyl)-1-pyrrolidinecarboxylate (D3; 800 mg, 2.94 mmol) was dissolved in methylene chloride (10 ml) and treated with trifluoroacetic acid (2.5 ml) for 2h. The reaction mixture was loaded as such on a SCX column and the non-basic compounds were washed away with methanol. The ninhydrine-positive fractions eluted with 1M methanolic ammonia were concentrated under vacuum at 40 °C for 30 min, isolating the title compound as a pale yellow oil: 410 mg, 2.92 mmol, 99% yield.
MS (ES/+): m/z = 141 $[M+H]^+$.
NMR (DMSO-d_6): δ (ppm) 3.69 (q, 1H), 3.62-3.45 (m, 3H), 3.45-3.35 (m, 2H), 2.52 (t, 1H), 2.13-1.96 (m, 2H), 1.85-1.72 (m, 1H), 1.50-1.37 (m, 1H).

Description 5
(9a*S*)-Hexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepin-2(3*H*)-one (D5)

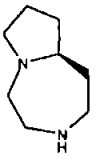


Methyl (2*S*)-2-pyrrolidinylacetate hydrochloride (1.08 g, 6.04 mmol) was dissolved in 20 ml of anhydrous dichloroethane. 1,1-Dimethylethyl (2-oxoethyl)carbamate (1.2 g, 7.25 mmol) was added, followed after 30 min by sodium triacetoxyborohydride (2.68 g, 12.08 mmol). The reaction was stirred for 3hrs at room temperature. The reaction mixture was diluted with methanol to obtain a clear solution, which was passed through a SCX cartridge. The product was eluted with 1 M methanolic ammonia. The solvent was removed under reduced pressure leaving the product as a pale-yellow oil. The crude was dissolved in methylene chloride (20 ml) and treated with trifluoroacetic acid (5 ml) for 1h. The reaction mixture was loaded as such on a SCX column and the non-basic compounds were washed away with methanol. The ninhydrine-positive fractions eluted with 1M methanolic ammonia were concentrated. The residue was redissolved in acetonitrile (20 ml) and stirred at 60°C for 2h. The solvent was removed under reduced pressure and the product purified by

chromatography (silica, CH_2Cl_2 / MeOH 95/5, Rf= 0.4) and isolated as a white solid: 315 mg, 2.04 mmol, 34% yield.
MS (ES/+): 155 $[M+H]^+$.
NMR (DMSO-d_6): δ (ppm) 7.50 (bs, 1H), 3.35-3.21 (m, 1H), 3.05-2.95 (m, 2H), 2.56-2.43 (m, 2H), 2.26-2.11 (m, 2H), 2.08-1.96 (m, 2H), 1.94-1.83 (m, 1H), 1.72-1.52 (m, 2H), 1.41-1.29 (m, 1H).
Rf: 0.2 (dichloromethane/methanol 95/5)

Description 6

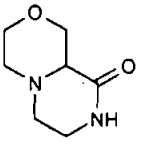
(9a*S*)-Octahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepine (D6)



Borane tetrahydrofuran complex solution (1M, 17.8 ml) was added to a solution of (9a*S*)-hexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepin-2(3*H*)-one (D5; 160 mg, 1.04 mmol) in tetrahydrofuran (5 ml) at 0°C and the mixture is stirred at room temperature for 30 min. HCl water solution 6N, 20 ml) was added slowly at 0°C and the solution was warmed at 60 °C for 4 hrs. The solvent was removed under reduced pressure and the product isolated by elution with 1M methanolic ammonia from a SCX cartridge (brownish oil, 120 mg, 83% yield).
MS (ES/+): m/z = 141 $[M+H]^+$.
NMR (DMSO-d_6): δ (ppm): 7.55 (bs, 1H), 3.65-3.09 (m, 3H), 3.08-2.82 (m, 2H), 2.55-2.39 (m, 2H), 2.38-2.27 (m, 1H), 2.27-2.09 (m, 1H), 2.08-1.79 (m, 2H), 1.78-1.48 (m, 2H), 1.47-1.27 (m, 2H).

Description 7

Hexahydropyrazino[2,1-*c*][1,4]oxazin-9(6*H*)-one (D7)



To a stirred suspension of N-Boc morpholine-2-carboxylic acid (991 mg, 4.29 mmol) in 10 ml of diethyl ether was added a solution of trimethylsilyldiazomethane (4 ml, 2M in hexanes, 8 mmol). After addition of methanol, the starting material went into solution and vigorous evolution of nitrogen was observed. After 1h 30 min., a TLC analysis showed complete disappearance of the starting material. The solvent was removed under reduced pressure, leaving the crude product as an oil (1.3 g), which contained both the expected methyl ester and the trimethylsilylmethyl ester (MS (ES/+): m/z=268 $[M+Na]^+$, 146 $[M-Boc]^+$, 340 $[M+TMS+Na]^+$, 218 $[M+TMS-Boc]^+$. The crude was dissolved in methylene chloride (10 ml) and treated with trifluoroacetic acid (2.5 ml) for 1h 30min. The free amine compounds were obtained collecting the ninhydrine-positive fractions eluted with 1M methanolic

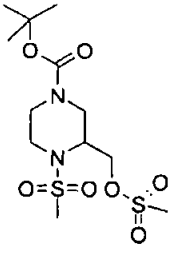
ammonia from a SCX column. After solvent removal, the crude (pale yellow oil, 670 mg, MS (ES/+): m/z=146 $[M+H]^+$, 218 $[M+TMS+H]^+$) was reacted with N-boc-2-aminoacetaldehyde (756 mg, 4.75 mmol) in anhydrous 1,2-dichloroethane (13 ml) in the presence of sodium triacetoxyborohydride (1.8 g, 8.44 mmol) for 16 h under nitrogen atmosphere. The reaction was diluted with methanol and loaded on a SCX column. The fractions eluted with 1 M methanolic ammonia were concentrated. The residual crude oil (880 mg, MS (ES/+): m/z=289 $[M+H]^+$, 361 $[M+TMS+H]^+$) was dissolved in anhydrous methylene chloride (12 ml) and treated with 4 ml of TFA for 30 min at 0°C and at room temperature for 3 h. The reaction mixture was loaded as such on a SCX column and the non-basic compounds were washed away with methanol. The ninhydrine-positive fractions eluted with 1M methanolic ammonia were concentrated. The residue was re-dissolved in methanol (20 ml) and stirred at 40°C for 30 min. The solvent was removed under reduced pressure and the product purified by chromatography (silica, CH_2Cl_2 / MeOH 95/5, Rf= 0.25) and isolated as a white solid: obtained 395 mg (2.53 mmol).

MS (ES/+): 157 $[M+H]^+$, 179 $[M+Na]^+$.

NMR ($CDCl_3$): δ (ppm) 5.77 (br.s, 1H); 4.32 (dd, 1H); 3.87 (br.d, 1H); 3.70 (t, 1H); 3.63 (td, 1H); 3.53 (t, 1H); 3.30-3.22 (m, 2H); 2.98-2.86 (m, 1H); 2.80 (d, 1H); 2.63 (td, 1H); 2.49 (td, 1H).

Description 8

1,1-Dimethylethyl 4-(methylsulfonyl)-3-{[(methylsulfonyl) oxy]methyl}-1-piperazinecarboxylate (D8)



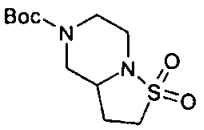
To a solution of 4.65 g of 1,1-dimethylethyl 3-(hydroxymethyl)-1-piperazinecarboxylate in 30 ml of dry dichloromethane, under N_2 at 0°C, 4.75 ml of TEA were added, followed by the slow addition of 3.7 ml of methanesulfonyl-chloride. After 12h of vigorous stirring at room temperature, reaction mixture was taken up with dichloromethane/H_2O, phases separated and the aqueous one back extracted with dichloromethane. Collected organics were dried over Na_2SO_4 and concentrated under vacuum to give crude material that was purified by chromatography on silica eluting with dichloromethane /MeOH from 100/0 to 90/10 to give 4 g of pure title material as colourless foam.

Rf (DCM/MeOH 9/1) = 0.8

^1H NMR ($CDCl_3$) δ: 1.48 (s, 9H), 2.96 (bs, 1H), 2.98 (s, 3H), 3.08 (s, 3H), 3.11 (bs, 1H), 3.2 (td, 1H), 3.71 (d, 1H), 4.02 (bs, 1H), 4.12 (bd, 1H), 4.23 (bm, 1H), 4.3 (bm, 1H), 4.4 (bm, 1H).

Description 9

1,1-Dimethylethyl hexahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (D9)



To a solution of 4 g of 1,1-dimethylethyl 4-(methylsulfonyl)-3-{[(methylsulfonyl) oxy]methyl}-1-piperazinecarboxylate (D8) in 50 ml of dry THF, under N_2 at -78°C, 11.8 ml of 1M secBu-Li in THF were added drop wise. After 30 min the mixture was allowed to slowly reach room temperature. After 2.5h the reaction was quenched with 20 ml of water, taken up with 100 ml of ethyl acetate and the phases separated. The aqueous one was back extracted with ethyl acetate (2 x 50 ml). Collected organics were dried over Na_2SO_4 and concentrated under vacuum to give crude material that was purified by chromatography on silica eluting with cyclohexaney/EtOAc from 7/3/ to 6/4 to get, after evaporation of the solvent, 2.438 g of pure title material as a white solid.

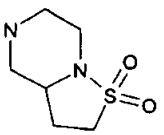
Rf (Cy/EA 1/1) = 0.45

MS (ES/+): 177 (M-Boc), 221 (M-iBu), 299 ($M+Na^+$).

^1H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 2.02 (m, 1H), 2.42 (m, 1H), 2.67 (bs, 1H), 2.81 (td, 1H), 2.95 (bs, 1H), 3.15 (m, 1H), 3.18 (m, 1H), 3.27 (td, 1H), 3.41 (d, 1H), 4.17 (b, 1H), 4.32 (b, 1H).

Description 10

Hexahydro-2*H*-isothiazolo[2,3-*a*] pyrazine 1,1-dioxide (D10)



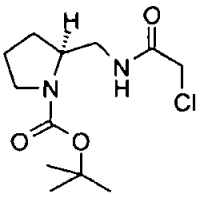
To a solution of 1.5 g of 1,1-dimethylethyl hexahydro-5*H*-isothiazolo[2,3-*a*]pyrazine-5-carboxylate 1,1-dioxide (D9) in 20 ml of dry dichloromethane, under N_2 at 0°C, 5 ml of TFA were added drop wise and left to react at 0°C for 1 h. Then reaction mixture was evaporated under vacuum and crude solid material purified by 50 g SCX cartridge, loading with DCM/MeOH, washing with DCM/MeOH then only with MeOH; product was recovered eluting with 1M NH_3 in MeOH. Solvent evaporation gave 0.95 g of pure title compound as white solid.

MS (ES/+): 177 $[M+H]^+$

^1H NMR ($CDCl_3$) δ: 1.97 (m, 1H), 2.36 (m, 1H), 2.59 (dd, 1H), 2.80 (dd, 2H), 3.1 (m. 3H), 3.19 (m, 2H), 3.41 (m, 1H).

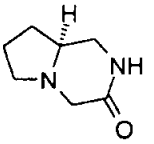
Description 11

1,1-Dimethylethyl (2*S*)-2-{[(chloroacetyl)amino]methyl}-1-pyrrolidinecarboxylate (D11)



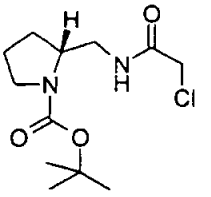
DIPEA (1.34 ml, 7.5 mmol) was added to a solution of 1,1-dimethylethyl (2*S*)-2-(aminomethyl)-1-pyrrolidinecarboxylate (1g, 5 mmol) in 50 ml of DCM; then chloroacetyl chloride (0.418 ml, 5.25 mmol) was slowly added and the reaction mixture stirred 1h before being worked up. DCM was added and the organic phase was washed with a saturated solution of ammonium chloride. The crude was purified by flash chromatography eluting with cyclohexane/ethyl acetate 8/2 affording 1.24 g of the target material.
MS (ES/+): 299-301 $[M + Na]^+$
NMR ($CDCl_3$): δ (ppm) 8.43-8.28 (br.s., 1H), 4.03 (s, 2H), 3.76-3.65 (m, 1H), 3.31-3.14 (m, 3H), 3.15-3.04 (m, 1H), 1.89-1.60 (m, 4H), 1.40 (s, (H).

Description 12
(8a*S*)-Hexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (D12)



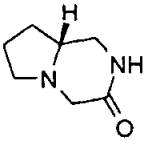
1,1-Dimethylethyl (2*S*)-2-{[(chloroacetyl)amino]methyl}-1-pyrrolidinecarboxylate (D11; 1.24, 4.5 mmol), was dissolved in 20 ml of DCM and treated with TFA (5 ml) at room temperature. After 1h complete conversion into the desired material was observed and the reaction mixture was loaded onto a SCX cartridge. The product obtained after elution with 2M NH_3 in MeOH was then dissolved in acetonitrile (30 ml) and treated with sodium carbonate (1.43 g, 10.34 mmol). The reaction mixture was heated at 60°C for 6 hours; the crude obtained after removal is purified by flash-chromatography eluting with dichloromethane/MeOH 95/5 affording 310 mg.
MS (ES/+): 141 $[M+H]^+$
NMR ($CDCl_3$): δ (ppm) 7.80-7.59 (br. s, 1H), 3.38 (d, 1H), 3.28-3.17 (m,1H), 2.99 (dt, 1H), 2.89 (t, 1H), 2.69 (d, 1H), 2.30-2.17 (m, 1H), 2.06-1.96 (m, 1H), 1.92-1.80 (m, 1H), 1.81-1.71 (m, 2H), 1.41-1.29 (m, 1H).

Description 13
1,1-Dimethylethyl (2*R*)-2-{[(chloroacetyl)amino]methyl}-1-pyrrolidinecarboxylate (D13)



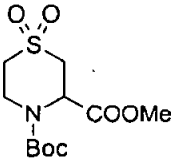
DIPEA (1.34 ml, 7.5 mmol) was added to a solution of 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-pyrrolidinecarboxylate (1 g, 5 mmol) in 50 ml of DCM; then chloroacetyl chloride (0.418 ml, 5.25 mmol) was slowly added and the reaction mixture stirred 1h before being worked up. DCM was added and the organic phase was washed with a saturated solution of ammonium chloride. The crude was purified by flash chromatography eluting with cyclohexane/ethyl acetate 8/2 affording 1.28 g of the target material.
MS (ES/+): 299-301 $[M + Na]^+$
NMR ($CDCl_3$): δ (ppm) 8.43-8.28 (br.s., 1H), 4.03 (s, 2H), 3.76-3.65 (m, 1H), 3.31-3.14 (m, 3H), 3.15-3.04 (m, 1H), 1.89-1.60 (m, 4H), 1.40 (s, (H).

Description 14
(8a*R*)-Hexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (D14)



1,1-Dimethylethyl (2*R*)-2-{[(chloroacetyl)amino]methyl}-1-pyrrolidinecarboxylate (D13; 1.24 g, 4.5 mmol), was dissolved in 20 ml of DCM and treated with TFA (5 ml) at room temperature. After 1h complete conversion into the desired material was observed and the reaction mixture was loaded onto a SCX cartridge. The product obtained after elution with 2M NH_3 in MeOH was then dissolved in acetonitrile (30 ml) and treated with sodium carbonate (1.43 g, 10.34 mmol). The reaction mixture was heated at 60°C for 6 hours; the crude obtained after removal is purified by flash-chromatography eluting with dichloromethane/MeOH 95/5 affording 250 mg of the desired compound.
MS (ES/+): 141 $[M+H]^+$
NMR ($CDCl_3$): δ (ppm) 7.80-7.59 (br. s, 1H), 3.38 (d, 1H), 3.28-3.17 (m,1H), 2.99 (dt, 1H), 2.89 (t, 1H), 2.69 (d, 1H), 2.30-2.17 (m, 1H), 2.06-1.96 (m, 1H), 1.92-1.80 (m, 1H), 1.81-1.71 (m, 2H), 1.41-1.29 (m, 1H).

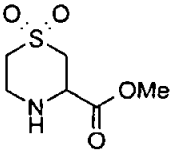
Description 15
4-(1,1-Dimethylethyl) 3-methyl 3,4-thiomorpholinedicarboxylate 1,1-dioxide (D15)



The preparation was done in two batches. In the first, to a stirred solution of 4-(1,1-dimethylethyl) 3-methyl 3,4-thiomorpholinedicarboxylate (WO 2001/040185) (936 mg, 3.59 mmol) in 3 ml of dichloromethane was added 55% 3-chloroperbenzoic acid (2.353 g, 7.50 mmol) at 0°C while stirring under nitrogen atmosphere. The reaction was allowed to reach room temperature in 1h. An additional aliquot of 55% 3-chloroperbenzoic acid (500 mg, 1.59 mmol) was added and the reaction stirred for 15 min. The reaction solution was washed with aqueous saturated sodium bicarbonate and sodium thiosulfate. The organic

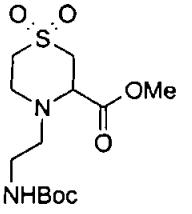
phase was dried over Na_2SO_4 and the solvent removed leaving the crude product, 1.01 g. In the second batch, the same procedure was applied to convert 714 mg (3.59 mmol) of 4-(1,1-dimethylethyl) 3-methyl 3,4-thiomorpholinedicarboxylate using 2.134 g of 55% 3-chloroperbenzoic acid (6.80 mmol) in 5ml of dichloromethane, obtaining 1.23 g of crude product. The combined crude reactions were purified by chromatography (silica, cyclohexane / ethyl acetate 70/30) to give 1.73 g of the target compound.
MS (ES/+): 316 $[M+Na]^+$, 194 $[M-Boc+1]^+$.
NMR (DMSO-d_6): δ (ppm) 5.55-5.17 (ms, 1H); 4.41-4.21(dt, 1H); 3.73-3.63 (m, 3H); 3.62-3.35 (m, 3H); 3.28-3.10 (td, 1H); 3.10-2.96 (dd, 1H); 1.56-1.24 (m, 9H).

Description 16
Methyl 3-thiomorpholinecarboxylate 1,1-dioxide (D16)



To a solution of 4-(1,1-dimethylethyl) 3-methyl 3,4-thiomorpholinedicarboxylate 1,1-dioxide (D15; 1.73 g, 5.9 mmol) in 17 ml of anhydrous methylene chloride, trifluoroacetic acid (4.2 ml) was added dropwise while stirring at 0°C under nitrogen atmosphere. The solution was stirred for 3h, while allowing it to reach room temperature. The solvent was removed under reduced pressure and the residue was loaded on a SCX cartridge, washed with methanol and eluted with 0.5M methanolic ammonia. The basic fractions were collected and the solvent removed leaving 1.08 g of the target product.
MS (ES/+): 194 $[M+Na]^+$.
NMR (DMSO-d_6): δ (ppm) 4.14-3.92 (br s, 1H); 3.84-3.70 (dd, 1H); 3.65-3.59 (s, 3H); 3.34-3.15 (m, 2H); 3.11-2.99 (m, 1H); 3.11-2.78 (m, 2H); 3.05-2.80 (m, 1H).

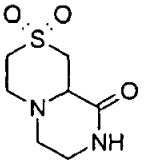
Description 17
Methyl 4-[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]-3-thiomorpholinecarboxylate 1,1-dioxide (D17)



To a stirred solution of methyl 3-thiomorpholinecarboxylate 1,1-dioxide (D16; 1.08 g, 5.6 mmol) in 14 ml of anhydrous 1,2-dichloroethane was added N-boc-2-aminoacetaldehyde (1.1 g, 6.7 mmol) and acetic acid (0.316 ml, 5.6 mmol). After 30 min. sodium triacetoxyborohydride (1.78 g, 8.4 mmol) was added and the solution stirred at room temperature. Additional aliquots of N-boc-2-aminoacetaldehyde and sodium triacetoxyborohydride (1.0 g, 4.7 mmol) were added and the reaction continued overnight.

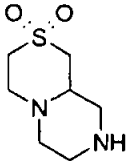
The solvent was removed under reduced pressure and the residue was purified by SCX column, followed by chromatography (silica, cyclohexane: ethyl acetate 70: 30 to 1:1) and again SCX, to give 295 mg of the target compound.
MS (ES/+): 337 $[M+1]^+$.
NMR (DMSO-d_6): δ (ppm) 6.77-6.55 (m, 1H), 4.17-4.08 (m, 1H), 3.69-3.57 (s, 3H), 3.48-3.31(m, 3H); 3.17-2.89 (m, 5H); 2.80-2.71 (m, 1H); 2.70-2.61 (m, 1H); 1.44-1.29 (s, 9H).

Description 18
Hexahydropyrazino[2,1-*c*][1,4]thiazin-9(6*H*)-one 2,2-dioxide (D18)



To a solution of methyl 4-[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]-3-thiomorpholinecarboxylate 1,1-dioxide (D17; 295 mg, 0.88 mmol) in 3 ml of anhydrous dichloromethane was added 1 ml of trifluoroacetic acid and the resulting solution was stirred at room temperature under nitrogen for 1h 30min. The solvent was removed under reduced pressure and the residue loaded on a SCX column, washed with methanol and eluted with methanolic ammonia. The product was purified further by chromatography (silica cartridge, cyclohexane to ethyl acetate, then dichloromethane to dichloromethane: methanol 70:30) to give 165 mg of the target compound.
MS (ES/+): 205 $[M+1]^+$.
NMR (DMSO-d_6): δ (ppm) 8.14-8.08 (br.s, 1H), 3.36-3.27 (m, 2H), 3.26-3.19 (m, 2H), 3.19-3.15 (m, 1H); 3.13-3.04 (m, 3H); 2.99-2.92 (dd, 1H); 2.68-2.61 (m, 1H); 2.59-2.52 (dt, 1H).

Description 19
Octahydropyrazino[2,1-*c*][1,4]thiazine 2,2-dioxide (D19)

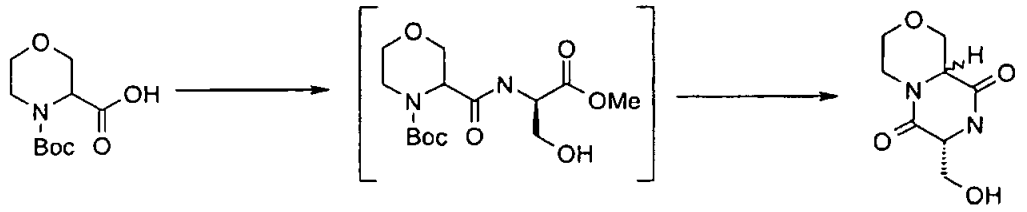


To a suspension of hexahydropyrazino[2,1-*c*][1,4]thiazin-9(6*H*)-one 2,2-dioxide (D18; 165 mg, 0.81 mmol) in 1 ml of anhydrous THF were added successive aliquots of a 1M solution of borane THF complex in THF (total 20.4 ml, 20.4 mmol) and the reaction stirred at room temperature and 50°C, until disappearance of the starting material. Hydrochloric acid (5M, 2 ml) was added to the solution and stirring was continued at 50°C for 12 h. The solvent was removed under reduced pressure and the residue loaded on a SCX cartridge, washed with methanol and eluted with 0.5M methanolic ammonia. The basic fractions were collected and the solvent removed leaving 172 mg of the target product, partially contaminated by the starting material.
MS (ES/+): 191 $[M+1]^+$.

NMR (CD3OD): δ (ppm) 3.50-2.70 (m, 13H); 2.42-2.33 (dt, 1H).

Description 20

(7*R*, 9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione and (7*R*, 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione (D20)



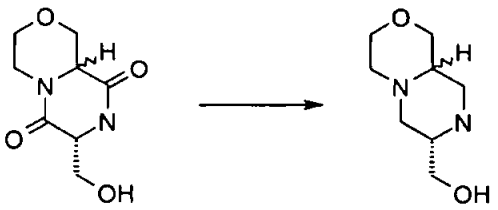
N-Boc morpholine 2-carboxylic acid (Astatech, 1.34 g, 5.80 mmol) was suspended in 15 mL of anhydrous dichloromethane, and treated with O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (2.4 g, 7.47 mmol) and diisopropylethylamine (2 mL, 11.47 mmol). The reaction was stirred for 40 min. A solution of D-serine methyl ester hydrochloride (1.8 g, 11.57 mmol) and diisopropylethylamine (2 mL, 11.47 mmol) in dichloromethane (15mL) was prepared and added to the reaction mixture. The reaction was left stirring at room temperature overnight. UPLC-MS analysis showed conversion to the product. The reaction was diluted with dichloromethane (40 mL) and extracted with sat. $NaHCO_3$ (2 x 40 mL), dried (Na_2SO_4), and the solvent was removed. The crude was taken to the next step without further purification.

It was dissolved in 20 mL of dichloromethane and treated with 10 mL of TFA. The reaction was striired at room temperature and checked by UPLC-MS after 4h which showed disappearance of the peak for the starting material, replaced by a new one for the deprotected species (m/z= 233, M+1). The reaction mixture was loaded as such on a SCX cartridge, washed with MeOH (4 column volumes) and eluted with 0.5 M methanolic ammonia. The basic, ninhydrin-positive fractions were collected and the solvent removed. The residue was dissolved in 10 mL of MeOH and stirred at 50°C under N_2 overnight (16h). The reaction was cooled down and a precipitate formed, which was collected by filtration to give 370 mg of the title compound. Direct MS: m/z= 223 (M+Na).

^{1}H-NMR: consistent with structure. Approx. 60:40 ratio of diastereoisomers:
1H NMR (400 MHz, DMSO-d_6) δ ppm 8.17 - 8.26 (s, 0.4 H) 8.09 - 8.17 (s, 0.6 H) 5.17 - 5.25 (m, 0.4 H) 5.09 - 5.17 (m, 0.6 H) 3.95 - 4.29 (m, 3 H) 3.60 - 3.91 (m, 3 H) 3.33 - 3.55 (m, 2 H) 2.61 - 2.90 (m, 0.6 H) 1.03 - 1.15 (t, 0.4 H).

Description 21

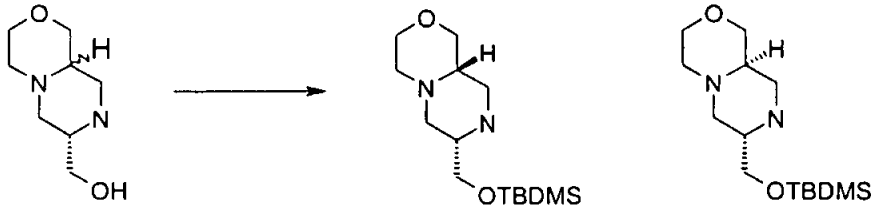
(7*S*, 9a*R*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol and (7*S*, 9a*S*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D21)



(7*R*, 9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione and (7*R*, 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione (D20) (365 mg, 1.82 mmol) was treated with 20 mL of 1M BH_3-THF solution at room temperature. The suspension was refluxed for 17 h and checked by direct MS, showing complete conversion to the product. It was cooled to 0°C, and 2 mL of MeOH were added slowly, followed by 1mL of conc. HCl (to pH <1). The solution was warmed to 70°C, stirred for 2 h and checked by direct MS. The solution was brought room temperature, the solvent removed and the residue taken up in MeOH (a few drops of water added), loaded on a SCX cartridge, washed with MeOH (5 column volumes) and eluted with 2M methanolic ammonia. The ninhydrin-positive fractions were collected and the solvent removed, leaving the title product as a clear oil. 320mg. Direct MS: m/z= 173 (M+1).
^{1}H-NMR consistent with structure, appears to be a mixture of diastereomers in approx. 60:40 ratio:
1H NMR (400 MHz, DMSO-d_6) δ ppm 4.50 - 4.59 (m, 0.4 H) 4.38 - 4.48 (m, 0.6 H) 2.96 - 3.74 (m, 6 H) 2.57 - 2.78 (m, 2 H) 2.34 - 2.41 (m, 2 H) 1.86 - 2.28 (m, 4 H) 1.69 (t, 1 H)

Description 22 and Description 23
(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D22) and

(7*S*,9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D23)



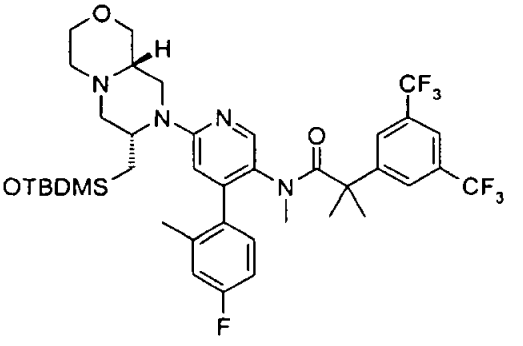
D22 D23

(7*S*, 9a*R*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol and (7*S*, 9a*S*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D21) (315 mg, 1.83 mmol) was dissolved in 10 mL of anhydrous dichloromethane and treated with Et_3N (600 µL, 4.30 mmol) and TDBMSCl (590 mg, 3.91 mmol). The reaction was stirred overnight at room temperature (17h). It was diluted with dichloromethane (30 mL) and extracted with sat. $NaHCO_3$ (2 x 20mL). TLC analysis (EtOAc : MeOH 95:5) showed 2 main products. The

organics were dried and the solvent removed leaving an oil, which was purified by flash chromatography (silica, EtOAc→EtOAc:MeOH 90:10). Isolated two products:
(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D22), 253 mg. Direct MS: m/z= 287 (M+1).
1H NMR (500 MHz, DMSO-d_6) δ ppm 3.72 - 3.79 (m, 1 H) 3.62 - 3.71 (m, 2 H) 3.37 - 3.56 (m, 2 H) 2.99 (t, 1 H) 2.65 - 2.78 (m, 1 H) 2.55 - 2.64 (m, 1 H) 2.25 - 2.44 (m, 3 H) 2.02 - 2.16 (m, 2 H) 1.90 - 2.02 (m, 1 H) 0.75 - 0.90 (s, 9 H) -0.05 - 0.05 (s, 6 H).
Identified as the *cis* isomer based on ROESY cross peaks.

(7*S*,9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D23), 202 mg. Direct MS: m/z= 287 (M+1).
1H NMR (500 MHz, DMSO-d_6) δ ppm 3.68 (d, 1 H) 3.56 (d, 1 H) 3.47 (t, 1 H) 3.36 - 3.43 (m, 2 H) 3.02 (t, 1 H) 2.68 - 2.76 (m, 1 H) 2.62 - 2.68 (m, 2 H) 2.50 - 2.56 (m, 1 H) 2.22 (t, 1 H) 2.11 - 2.18 (m, 1 H) 1.90 - 1.97 (m, 1 H) 1.70 (t, 1 H) 0.84 (s, 9 H) 0.02 (s, 6 H)
Identified as the *trans* isomer based on ROESY cross peaks.

Description 24
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D24)



Method a):
(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D22) (250 mg, 0.872 mmol) was dissolved in 3.8 mL of toluene. To this solution was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (460 mg, 0.863 mmol), followed by bis-tri –tert-butylphosphine palladium (110 mg, 0.215 mmol), hexadecyltrimetylammonium chloride (45 µL of a 25% aqueous solution) and sodium hydroxide solution (85 µL of a 50% aqueous solution, 0.85 mmol). The solution was degassed by 3 freeze-pump-thaw cycles, then stirred at 90°C. After 4h, UPLC/MS analysis indicated conversion to the target compound and no trace of starting chloropyridine. The reaction was brought to room temperature, diluted with EtOAc (20 mL) and washed with sat. $NaHCO_3$ (10 mL). The organics were dried and the solvent evaporated. The product was isolated by flash chromatography (cyclohexane -> cyclohexane:EtOAc 85:15) as a

60

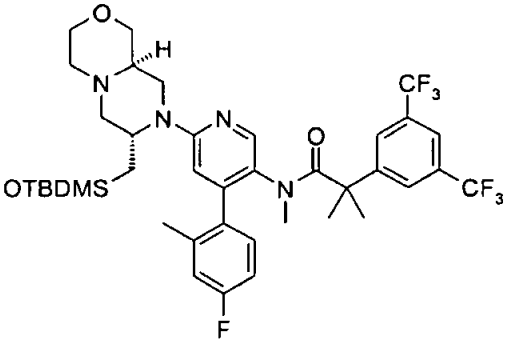
white solid: 390 mg (0.498 mmol, 57%) taken to the next step without further characterization.

Method b):

To a stirred solution of (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D107, 5g, 17.45 mmoles) in 150 ml of dry toluene at room temperature under nitrogen, a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (7.75g, 14.54 mmoles) in 50 ml of dry toluene was added, followed by sodium *tert*-butoxide (2.1g, 21.81 mmoles) and bis(tri-*tert*-butyl phosphine) palladium (1.49g, 2.908 mmoles). The resulting mixture was heated at reflux temperature for 4 hours. The mixture was allowed to cool down to room temperature and filtered over Sterimat. The filtrate was then diluted with ethyl acetate (200ml) and with sodium hydrogen carbonates (sat. solution, 200 ml). Phases were separated and the aqueous layer was extracted with ethyl acetate (2 x 150 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to a residue, purified by silica gel chromatography eluting with 10 to 20% EtOAc/Cyclohexane to afford the title compound as pale yellow foam (10.1g).
UPLC/MS: peak at Rt = 1.26 min with m/z = 783.35 $[M+H]^+$
HPLC (walk-up): Rt = 6.98 min (area % = 98.22)

Description 25

2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*S*,9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D25)

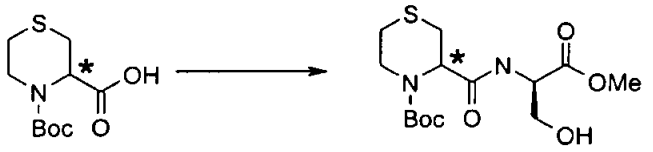


(7*S*,9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D23) (140 mg, 0.489 mmol) was dissolved in 2 mL of toluene. To this solution was added the 2-chloropyridine (236 mg, 0.444 mmol), followed by bis-tri –tert-butylphosphine palladium (60 mg, 0.117 mmol), hexadecyltrimetylammonium chloride (25 µL of a 25% aqueous solution) and sodium hydroxide solution (45 µL of a 50% aqueous solution). The solution was degassed by 3 freeze-pump-thaw cycles, then stirred at 90°C. UPLC/MS analysis after 4h indicated only partial conversion to the target compound. More catalyst (20 mg, 0.039 mmol) was added and the reaction left at the same temperature for

additional 2h, but no change was observed in the conversion to product. The solution was diluted with with EtOAc (20 mL) and washed with sat. $NaHCO_3$ (10 mL).The product was isolated by flash chromatography (cyclohexane:EtOAc 94:6 -> 50:50) as a pale yellow oil: 87 mg (0.111 mmol, 23%) taken to the next step without further characterization.

Description 26

1,1-dimethylethyl (3*R* or *S*)-({[(1*R*)-1-(hydroxymethyl)-2-(methyloxy)-2-oxoethyl]amino}carbonyl)-4-thiomorpholinecarboxylate (non-preferred name) (D26)-Diastereoisomer 1



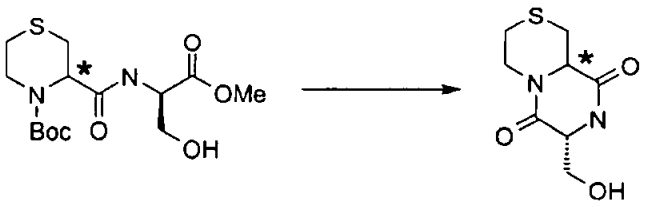
To a solution of N-Boc thiomorpholine carboxylic acid (0.488 g, 1.97 mmol) and *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (0.697 g, 2.17 mmol) in 5 mL of anhydrous dichloromethane was added DIPEA (0.7 mL, 3.95 mmol) and the solution was stirred for 30 mins. To a suspension of D-serine methyl ester hydrochloride (0.47 g, 3.95 mmol) in 5 mL of anhydrous dichloromethane was added DIPEA (0.7 mL, 3.95 mmol) and the resulting solution was stirred for 30 mins. Then the solution containing the serine free base was added to the reaction mixture and it was left stirring at room temperature overnight.

Water was added to the reaction mixture and the two phases were separated. The aqueous layer was extracted with dichloromethane (3X) and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness. This crude material (1.66 g) was used in the next step without further purification.

UPLC-MS: m/z= 349 (M+1) @ t=0.59 min

Description 27

(7*R*, 9a*R* *or* 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione (D27)-Diastereoisomer 1 of (D32)



To a solution of the crude 1,1-dimethylethyl (3*R* or *S*)-({[(1*R*)-1-(hydroxymethyl)-2-(methyloxy)-2-oxoethyl]amino}carbonyl)-4-thiomorpholinecarboxylate (D26) in 20 mL of dichloromethane were added 10 mL of TFA. The reaction mixture was stirred at room

temperature for 4hrs. The solvent was removed under reduced pressure and the residue was taken up in MeOH and loaded on a SCX cartridge. The fractions eluted with methanolic ammonia were collected, the volume was reduced and the solution was stirred at 50°C for 45 min. Then it was irradiated three times by microwave [set parameters: T=80°C, t=10 min (1X); T=120°C, t=5 min (2X)]. The solvent was removed and after 2 days the crude revealed the formation of a white solid. So it was precipitated with DME and it was collected by filtration, washing with Et_2O, to give the 1st batch of the title compound (120 mg, y=28% over 2 steps). The filtered solution was evaporated to dryness and the resulting crude, dissolved in DME, was irradiated two times by microwave (set parameters: T=130°C, t=30 min). After filtration, the 2nd batch of the title compound was isolated as a brownish solid (94 mg, y=22% over 2 steps). The filtered solution was treated in the same way as before and after four microwave irradiation [set parameters: T=130°C, t=30 min (3X) and t=90 min (1X)] the 3rd batch of the title compound was isolated as a brownish solid (50 mg, y=12% over 2 steps).

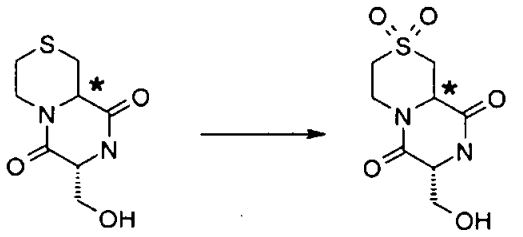
Since the purity of these three batches was very similar by NMR analysis, all of them were used in the next step.

UPLC/MS: m/z= 217 (M+1) @ t=0.36 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.03 - 8.27 (m, 1 H) 5.04 (t, 1 H) 4.73 (td, 1 H) 3.98 (dd, 1 H) 3.86 - 3.90 (m, 1 H) 3.72 - 3.79 (m, 1 H) 3.47 - 3.57 (m, 1 H) 2.90 (d, 1 H) 2.80 (d, 1 H) 2.73 - 2.81 (m, 1 H) 2.45 - 2.64 (m, 2 H)

Description 28

(7*R*, 9a*R* or 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione 2,2-dioxide (D28)-Diastereoisomer 1 of (D33)



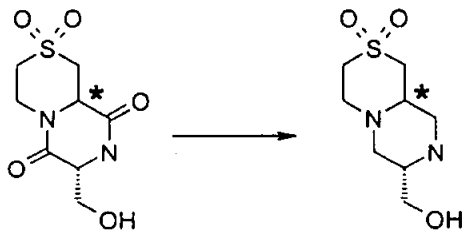
To a suspension of the starting (7*R*, 9a*R* *or* 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione (D27) (264 mg, 1.22 mmol) in dichloromethane (5 mL) was added 77% m-CPBA (684 mg, 3.05 mmol) and the reaction mixture was stirred at room temperature for 3 hrs. The solvent was removed and the crude was purified by chromatography (silica, CH_2Cl_2: 2M NH_3 in MeOH 95:5 to 8:2) to give the title compound as a white solid (200 mg, y=66%).

HPLC/MS: m/z= 249 (M+1) @ t=0.21 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.34 - 8.47 (m, 1 H) 5.11 (t, 1 H) 4.80 (dt, 1 H) 4.25 (dd, 1 H) 3.89 - 3.99 (m, 1 H) 3.72 - 3.84 (m, 1 H) 3.62 (t, 1 H) 3.49 - 3.59 (m, 1 H) 3.23 - 3.37 (m, 2 H) 3.13 (t, 1 H) 3.01 (t, 1 H)

Description 29

[(7*S*, 9a*R* or 9a*S*)-2,2-dioxidooctahydropyrazino[2,1-c][1,4]thiazin-7-yl]methanol (D29)-Diastereoisomer 1 of (D34)



To a solution of the starting (7*R*, 9a*R* or 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione 2,2-dioxide (D28) (200 mg, 0.806 mmol) was added 8.06 mL of 1M BH_3-THF solution at room temperature. The suspension was refluxed overnight and checked by UPLC/MS.

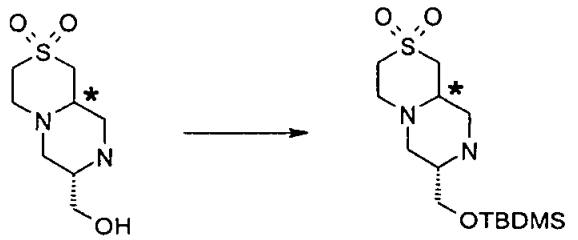
HCl 6 N (ca. 8 mL) was added to the reaction mixture, cooled to 0°C, and the resulting solution was refluxed for 1 hr. The crude was purified by SCX cartridge to give the title compound as a white solid (182 mg, quantitative yield)

HPLC/MS: m/z= 221 (M+1) @ t=0.17 min

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.56 (t, 1 H) 3.18 - 3.26 (m, 2 H) 2.94 - 3.15 (m, 4 H) 2.72 - 2.80 (m, 3 H) 2.56 - 2.64 (m, 1 H) 2.44 - 2.53 (m, 1 H) 2.22 - 2.36 (m, 2 H) 1.74 (t, 1 H)

Description 30

(7*S*, 9a*R* or 9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-c][1,4]thiazine 2,2-dioxide (D30)-Diastereoisomer 1



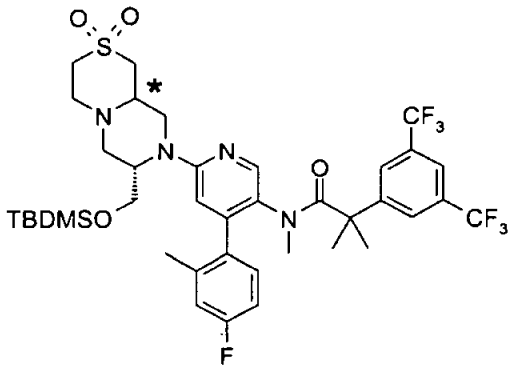
To a suspension of [(7*S*, 9a*R* or 9a*S*)-2,2-dioxidooctahydropyrazino[2,1-*c*][1,4]thiazin-7-yl]methanol (D29) (182 mg, 0.818 mmol) in 8 mL of anhydrous dichloromethane was added Et_3N (340 µL, 2.45 mmol) and TDBMSCl (246 mg, 1.64 mmol). The reaction mixture was stirred for 15 hrs at room temperature and then the homogeneous solution was left still for 2 days.

Sat. $NaHCO_3$ was added and the two phases were separated. The aq. layer was extracted with dichloromethane (3X) and the combined organic phases were dried with Na_2SO_4 and

evaporated to dryness. The crude was purified by chromatography (silica, CH_2Cl_2: MeOH 1:0 to 99:1) to give the title compound as a white solid (150 mg, y=55%).
UPLC/MS: m/z= 335 (M+1) @ t=0.54 min
1H NMR (400 MHz, DMSO-d_6) δ ppm 3.39 - 3.48 (m, 1 H) 3.31 - 3.40 (m, 1 H) 3.13 (t, 1 H) 2.91 - 3.09 (m, 3 H) 2.70 - 2.85 (m, 3 H) 2.56 - 2.65 (m, 1 H) 2.42 - 2.51 (m, 1 H) 2.27 - 2.36 (m, 1 H) 2.19 - 2.30 (m, 1 H) 1.91 - 2.06 (m, 1 H) 1.74 (t, 1 H) 0.80 (s, 9 H) -0.02 (s, 6 H)

Description 31

2-[3,5-bis(trifluoromethyl)phenyl]-N-[6-[(7*S*, 9a*R* or 9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D31)-Diastereoisomer 1

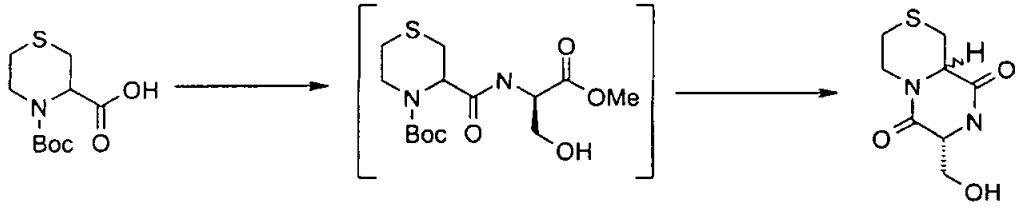


To a solution of (7*S*, 9a*R* *or* 9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]thiazine 2,2-dioxide (D30) (147 mg, 0.44 mmol) and 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (180 mg, 0.338 mmol) in 3 mL of anhydrous toluene were added bis-tri–tert-butylphosphine palladium (34.5 mg, 0.068 mmol), hexadecyltrimetylammonium chloride (21.6 µL of a 25% aqueous solution) and sodium hydroxide solution (40 µL of a 50% aqueous solution). The reaction mixture was degassed by freeze-pump-thaw cycles and then it was stirred at 90°C for 12 hrs. During this reaction time further amounts of the palladium catalyst (17+17 mg) were added. EtOAc and $NaHCO_3$ were added to the reaction mixture and the two phases were separated. The aqueous phase was extracted with EtOAc (3X) and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The crude was purified by chromatography (silica, cyclohexane:EtOAc 9:1 to 75:25) to give the title compound as a white solid (172 mg, yield=47%).
MS: m/z= 831 (M+1) and 416 ($^M/_2$ +1)
HPLC/MS: m/z= 831 (M+1) and 416 ($^M/_2$ +1) @ t=1.22 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.86 (s, 1 H) 7.60 - 7.82 (m, 2 H) 7.16 (d, 1 H) 6.98 - 7.14 (m, 2 H) 6.67 (s, 1 H) 4.36 - 4.54 (m, 1 H) 3.91 - 4.12 (m, 1 H) 3.80 - 3.94 (m, 1 H) 3.58 - 3.73 (m, 1 H) 3.08 - 3.47 (m, 5 H) 2.87 - 3.00 (m, 1 H) 2.72 - 2.82 (m, 1 H) 2.51 (s, 3 H) 2.42 - 2.67 (m, 3 H) 2.19 (s, 3 H) 1.49 (s, 3 H) 1.34 (s, 3 H) 0.78 (s, 9 H) 0.00 (s, 6 H)

Description 32

(7R, 9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione and (7R, 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione (D32)

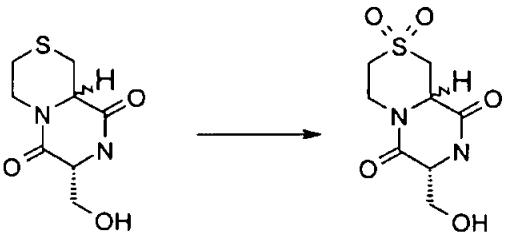


To a solution of N-Boc thiomorpholine carboxylic acid (0.803 g, 2.96 mmol) in 16 mL of anhydrous dichloromethane was added *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) (1.03 g, 3.22 mmol) and the solution was stirred for 45 min. A solution of D-serine methyl ester hydrochloride (0.911 g, 5.85 mmol) and Huenig's base (1.02 mL, 5.85 mmol) in dichloromethane was prepared and added to the reaction mixture. The reaction was left stirring at room temperature overnight. UPLC-MS analysis showed conversion to the product. The reaction was diluted with dichloromethane and extracted with water, dried (Na_2SO_4), and the solvent was removed. The crude (1.73 g) was taken to the next step without further purification.

It was dissolved in 60 mL of dichloromethane and added 15 mL of TFA at 0°C. The reaction stirred at room temperature for 2h. The solvent was removed under reduced pressure and the residue was taken up in MeOH and loaded on a SCX cartridge. The fractions coming from SCX were collected, the solvent removed and the residue dissolved in methanol and stirred at 50°C overnight, then at 90°C for 21h. The reaction was cooled down kept in a freezer. The precipitate that formed was collected by filtration and the mother liquour concentrated by removing the colvent. The two fractions were analysed by ^{1}H-NMR, which was consistent with the product, as a mixture of diastereoisomers. They were combined and used in the next step without further purification.

Description D33

(7*R*, 9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione 2,2-dioxide and (7*R*, 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione 2,2-dioxide (D33)

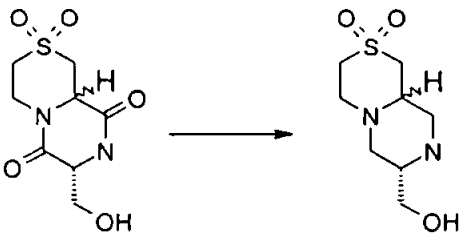


To a suspension of (7R, 9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione and (7R, 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione (D32) (851 mg, 3.94 mmol) in dichloromethane (17 mL), was added 77% m-CPBA (2.21 g, 9.84 mmol) and the reaction was left at room temperature for 2h. A precipitate formed and was separated and washed with MeOH. The liquid phase was concentrated. The product was isolated by flash chromatography (CH_2Cl_2 -> CH_2Cl_2: 0.5M NH_3 in MeOH 85:15), obtaining 594 mg, 2.39 mmol.

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.44 (s, 1 H) 8.41 (s, 1 H) 5.48 (t, 1 H) 5.12 (t, 1 H) 4.80 (dt, 1 H) 4.70 – 4.76 (m, 2H) 4.37 (dd, 1H) 4.25 (dd, 1 H) 4.07 – 4.12 (m, 1 H) 3.89 - 3.99 (m, 1 H) 3.72 - 3.85 (m, 2 H) 3.62 (t, 1 H) 3.52 - 3.57 (m, 1 H) 3.23 - 3.47 (m, 4 H) 2.95 – 3.18 (m, 6 H). Mixture of diastereoisomers (ratio about 55/45).

Description 34

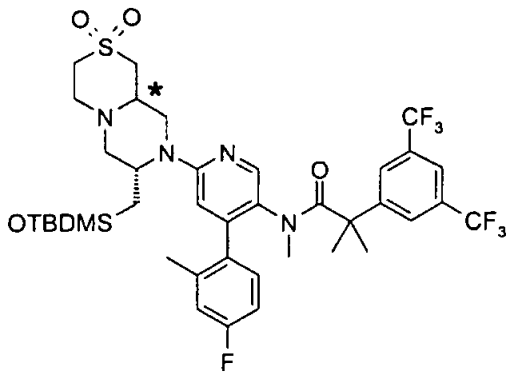
[(7*S*, 9a*R*)-2,2-dioxidooctahydropyrazino[2,1-c][1,4]thiazin-7-yl]methanol and [(7*S*, 9a*S*)-2,2-dioxidooctahydropyrazino[2,1-c][1,4]thiazin-7-yl]methanol (D34)



To (7*R*, 9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione 2,2-dioxide and (7*R*, 9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]thiazine-6,9-dione 2,2-dioxide (D33) (592 mg, 2.39 mmol) was added 24 mL of 1M BH_3-THF solution at room temperature. The suspension was refluxed overnight, and checked by UPLC/MS: product peaks seen at 0.17 and 0.37 min, both with m/z= 221 (M+1).The excess BH_3 was quenched by addition of MeOH (10 mL) at 0°C, followed by conc. HCl (2mL) and the solution was heated to 80°C and stirred for 4 h. The crude was purified by SCX cartridge, leaving the expected product: 398 mg, 1.81 mmol.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.50 (t, 1 H) 4.60 (t, 1 H) 3.33 - 3.43 (m, 2 H) 2.99 - 3.29 (m, 12 H) 2.75 - 2.93 (m, 2 H) 2.56 - 2.72 (m, 2 H) 2.25 - 2.38 (m, 3 H) 1.76 (t, 1 H). The sample consists of a mixture of diastereoisomers (ratio about 60/40).

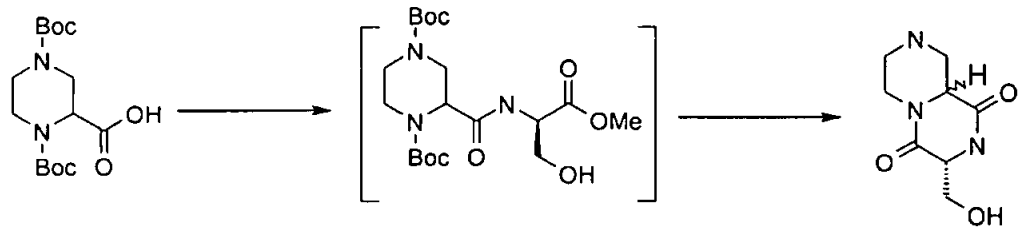
Description 35 and Description 30



To a solution of (7*S*, 9a*S* or *R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-c][1,4]thiazine 2,2-dioxide (D35) (111 mg, 0.331 mmol) in 2.2 mL of toluene was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (136 mg, 0.254 mmol), bis-tri –tert-butylphosphine palladium (26 mg, 0.051 mmol), hexadecyltrimetylammonium chloride (16 µL of a 25% aqueous solution) and, at last, sodium hydroxide solution (31 µL of a 50% aqueous solution). The solution was degassed by freeze-pump-thaw cycles, then stirred at 90°C for 3.5 h. A check by UPLC/MS showed the product peak at 1.22 min., m/z = 831 (M+1), 416 ($^{M}/_{2}$ +1). The solution was diluted with with EtOAc, washed with sat. $NaHCO_3$, and the organics dried (Na_2SO_4). The product was isolated by flash chromatography (cyclohexane:EtOAc 100:0 -> 40:60): 160 mg (0.192 mmol) taken to the next step without further characterization.

Description 37

(3*R*, 9a*R*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione and (3*R*, 9a*S*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D37)



To a solution of 1,4-bis{[(1,1-dimethylethyl)oxy]carbonyl}-2-piperazinecarboxylic acid (10.88 g, 32.93 mmol) in 100 mL of dichloromethane was added *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) (11.62 g, 36.19 mmol) and diisopropylethylamine (8.6 mL, 54.28 mmol). The reaction was stirred for 1 h. In the meantime, a solution of D-serine methyl ester hydrochloride (10.24 g, 65.81 mmol) and diisopropylethylamine (11.50 mL, 65.9 mmol) in dichloromethane was prepared and finally added to the reaction mixture. The reaction was left stirring at room temperature for 2.5 h. UPLC-MS analysis showed no more starting material and conversion to the product (peak

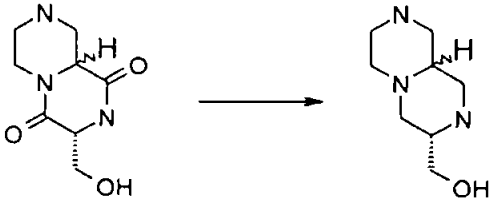
at 0.67 min, m/z = 432, M+1). The reaction was diluted with dichloromethane and extracted with sat. $NaHCO_3$, dried (Na_2SO_4), and the solvent removed. The crude (23.5 g) was taken to the next step without further purification.

It was dissolved in 80 mL of dichloromethane and treated with 20 mL of TFA, added at 0°C. The reaction was stirred at room temperature for 2h, stored in a freezer overnight, and then added again with 10 mL of TFA and stirred at room temperature for 8h. It was stored again in freezer, then added more TFA (20mL) and stirred at room temperature for 5h. After addition at 0°C of 30 mL of TFA and heating at 30°C for 3h, the reaction appeared by UPLC/MS not to contain starting material anymore. Product seen at 0.20 min, m/z = 232 (M+1). The reaction volume was reduced by evaporation and the crude was purified by SCX. The basic fractions were stirred at 50°C overnight. The solution was concentrated and the solid residue triturated with MeOH (5mL) and diethyl ether, leaving 4.44 g of product. Mixture (2:1) of two diastereomers.

1H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 - 8.07 (s, 0.66 H) 7.98 - 8.02 (s, 0.33 H) 5.00 - 5.21 (m, 1 H) 4.14 - 4.33 (m, 1 H) 3.67 - 3.89 (m, 3 H) 3.41 - 3.55 (m, 1 H) 3.10 - 3.29 (m, 2 H) 2.76 - 2.94 (m, 1 H) 2.26 - 2.68 (m, 3 H).

Description 38

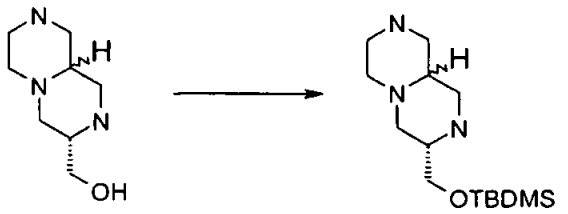
(3*S*, 9a*R*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol and (3*S*, 9a*S*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol (D38)



(3*R*, 9a*R*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione and (3*R*, 9a*S*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D37)(4.44 g, 22.28 mmol) was divided into two equal portions. Each portion was treated at 0°C with 110 mL of 1M BH_3-THF solution and brought to reflux (80°C) for 24h. The reaction was checked by direct UPLC/MS and was not complete. A further aliquot of 50 mL of 1M BH_3-THF solution was added to each reaction, and they were kept at 80°C for additional 16 h. They were checked again by MS and found to be complete (for both m/z= 172, M+1). The reaction flasks were cooled to -10°C and treated with 30 mL of 6M HCl. The resulting solutions were warmed to 80°C and stirred for 3.5 h. Both reactions were checked by direct MS (m/z= 172, M+1 for both samples). The reaction mixture was purified by SCX, obtaining 4.07 g of product. 1H NMR consistent with the structure, mixture of diastereoisomers.

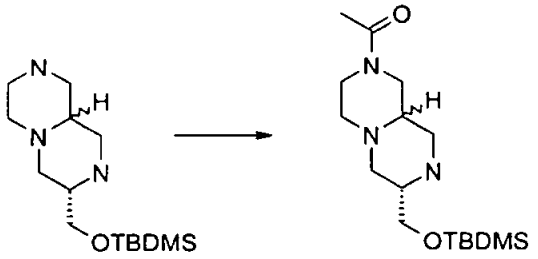
Description 39

(3*S*, 9a*R*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine and (3*S*, 9a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-a]pyrazine (D39)



(3*S*, 9a*R*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol and (3*S*, 9a*S*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol (D38) (4.065 g, 23.75 mmol) was dissolved in 100 mL of dichloromethane and treated with Et_3N (9.32 mL, 71.25 mmol) and TDBMSCl (8.4 g, 59.38 mmol). The reaction was stirred at room temperature for 70 h. It was checked by UPLC/MS, which showed conversion to product: peaks at 0.45 and 0.46 min, m/z = 286 (M+1). It was diluted with dichloromethane, extracted with sat. $NaHCO_3$ and brine, and the dried over Na_2SO_4. The crude was purified by flash chromatography (silica, CH_2Cl_2 -> CH_2Cl_2: MeOH 80:20), to give 4.410g of the expected product.
Spectrum consistent with the product. Mixture of diastereomers, roughly 2:1 ratio.
1H NMR (400 MHz, DMSO-d_6) δ ppm 3.67 - 3.81 (m, 1 H) 3.35 - 3.48 (m, 1 H) 2.58 - 2.84 (m, 5 H) 2.18 - 2.58 (m, 3 H) 1.93 - 2.17 (m, 2 H) 1.74 - 1.93 (m, 1 H) 1.63 - 1.74 (m, 1 H) 0.87 (s, 3 H) 0.86 (s, 6 H) 0.04 (2, 2 H) 0.02 (s, 4 H).

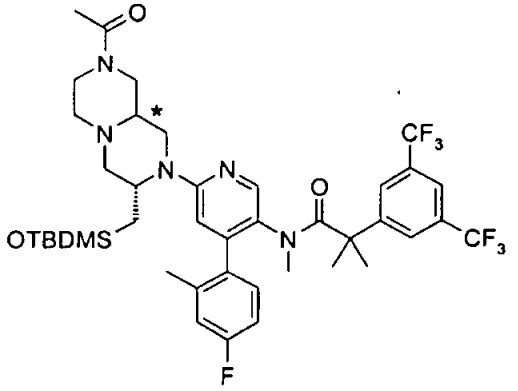
Description 40
(7*S*, 9a*R*)-2-acetyl-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine and (7*S*, 9a*S*)-2-acetyl-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D40)



To a solution of (3*S*, 9a*R*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine and (3*S*, 9a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-a]pyrazine (D39) (4.407 g, 15.44 mmol) in 100 mL of dichloromethane was added triethylamine (3.23 mL , 23.16 mmol) and it was brought to – 50 °C. A solution of acetic anhydride (1.459 mL, 15.44 mmol) in 16 mL of dichloromethane was added dropwise in 45 min. The reaction was stirred at– 50 °C for additional 30 min. and then let back to room temperature. The reaction was checked by UPLC/MS, which showed the two diasereomeric products at 0.54 and 0.57 min, m/z = 328 (M+1). The reaction mixture was diluted with dichloromethane, extracted with sat. $NaHCO_3$ and brine, and the dried over Na_2SO_4. The crude was purified by flash chromatography (silica, CH_2Cl_2 -> CH_2Cl_2: 0.5 M NH_3 in MeOH 90:10), obtaining 4.334 g.
1H NMR (400 MHz, DMSO-d_6) indicated a mixture of diastereoisomers withdiagnostic peaks at 0.05 ppm, and 0.03 ppm.

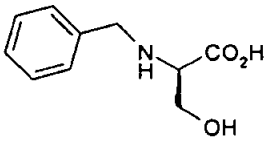
Description 41 and Description 42
***N*-[6-[(3*S*, 9a*R* or *S*)-8-acetyl-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D41)-Diastereoisomer 1 and**

***N*-[6-[(3*S*, 9a*S* or *R*)-8-acetyl-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D42)-Diastereoisomer 2**



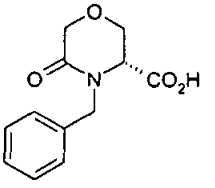
To a solution of (7*S*, 9a*R*)-2-acetyl-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine and (7*S*, 9a*S*)-2-acetyl-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D40) (1.5 g, 5.72 mmol) in 20 mL of toluene was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (2.034 g, 3.816 mmol), bis-tri –tert-butylphosphine palladium (440 mg, 0.86 mmol), hexadecyltrimetylammonium chloride (73 µL of a 25% aqueous solution) and, at last, sodium hydroxide solution (456 µL of a 50% aqueous solution). The solution was degassed by two freeze-pump-thaw cycles, then stirred at 90°C for 4 h. More bis-tri –tert-butylphosphine palladium (187 mg, 0.37 mmol) was added and the reaction stirred at 90°C for additional 4 h. The reaction was checked by UPLC/MS, which showed peaks for the expected products at 0.93 and 1.17 min., m/z = 824 (M+1) for both. The solution was diluted with EtOAc, washed with sat. $NaHCO_3$, brine, and the organics dried (Na_2SO_4). The products were isolated by flash chromatography (cyclohexane:EtOAc 70:30 -> 0:100).
(D41) Diastereoisomer 1, 1.1686 g, UPLC/MS: peak at 1.17 min, m/z = 824. M+1.
(D42) Diastereoisomer 2, 1.0916 g, UPLC/MS: peak at 0.93 min, m/z = 824. M+1.

Description 43: *N*-(phenylmethyl)-D-serine (D43)



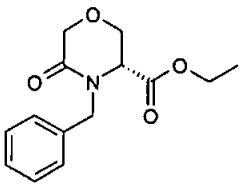
The title compound was made according to the procedure described G.R. Brown, J. Chem. Soc. Perkin Trans 1, 1985, 2577. Benzaldehyde (10.16mL,0.1mol) was added to a vigorously stirred solution of D-Serine (10.47g, 0.1mol) in 2N NaOH solution (50mL), stirred for 30 minutes at R.T. before cooling in an ice-salt bath to ~6°C before adding Sodium Borohydride (1.06g, 27.90mmol) portionwise over 40 minutes. The reaction was stirred at R.T. for 1 hour before adding more benzaldehyde (10.16mL, 0.1mol) and cooling down in an ice-salt bath to between 6-10°C and then adding more sodium Borohydride (1.06g, 27.90mmol) portionwise over 45 minutes. The reaction mixture was stirred at R.T. for 2 hours, washed with Et_2O. Made sure all solid material in solution, hence diluted with water before washing with Et_2O x2. Aqueous layer acidified to ~pH 6.5, using c.HCl solution. Solid precipitated out. Filtered, dried in the vacuum oven overnight at 40°C to afford a white solid in 46% yield.
NMR (DMSO-d6) δ 7.44-7.30 (5H, m), 3.98 (2H, q), 3.73- 3.61 (1H, m), 3.14 (1H, m).

Description 44: (3*R*)-5-oxo-4-(phenylmethyl)-3-morpholinecarboxylic acid (D44)



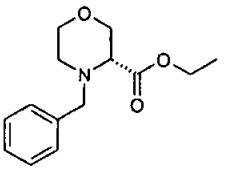
The title compound was prepared according to the method described by H.H. Otto, Helvetica Chimica Acta, 2004, 87, 90. To an ice cooled solution of N-(phenylmethyl)-D-serine (8.90g, 45.59mmol) in 2N NaOH solution (50mL) was added chloroacetyl chloride (4.36mL, 54.71mmol), dropwise over 15 minutes. The reaction was stirred for 30 minutes before adding 30% NaOH solution (4.5g in 15mL) and stirring at R.T. for 2 and ½ hours. It was cooled in an ice bath before adding c.HCl solution to pH<1. solid precipitated out. Filtered. Suspended in isopropanol and heated at reflux for 10 minutes. Filtered hot. Solvent evaporated to afford a pale yellow solid. Triturated with Et_2O to afford the title compound as a cream solid in 29% yield.
MS (API+): m/z 236.1 (MH+: 100%) @ retention time 1.61min

Description 45: Ethyl (3*R*)-5-oxo-4-(phenylmethyl)-3-morpholinecarboxylate (D45)



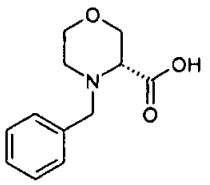
The title compound was prepared according to the procedure described by H.H.Otto, Helvetica Chimica Acta, 2004, 87, 90 using (3*R*)-5-oxo-4-(phenylmethyl)-3-morpholinecarboxylic acid (D44, 3.13g, 13.33mmol) in EtOH (30mL), cooling in an ice bath before adding Thionyl Chloride (1.46mL) dropwise, and then stirring at R.T. for 6hours. Added more thionyl chloride (1mL) and stirring at R.T. overnight. Added more thionyl chloride (1mL) and stirred for 4 hours, added further thionyl chloride (0.5mL) and stirred overnight again. Added thionyl chloride (0.2mL) and left stirring for 5 hours. Solvent evaporated to afford the title compound as an orange oil in quantative yield.
MS (API+): m/z 264.1 (MH+; 100%) @ retention time 2.28 min
$[\alpha]_D$ = – 11.4°, where l = 1cm, c = 0.5 in DCM

Description 46:Ethyl (3*R*)-4-(phenylmethyl)-3-morpholinecarboxylate (D46)



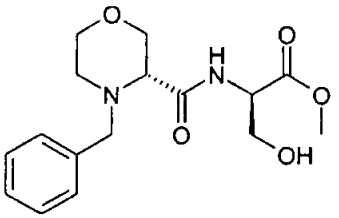
The title Compound was prepared according to the procedure used by G.R.Brown, J. Chem. Soc. Perkin Trans 1, 1985, 2577, using ethyl (3*R*)-5-oxo-4-(phenylmethyl)-3-morpholinecarboxylate (D45, 3.64g, 13.84mmol) in dry THF (70mL), cooled in an ice bath before adding borane-dimethylsulphide complex (1.84mL, 10M), slowly. The reaction mixture was allowed to warm up to room temperature overnight. Stirred for further six hours, added more borane-dimethylsulphide complex and stirred at R.T. over the weekend. Reaction quenched carefully with water, dropwise till the effervescence had finished. Solvent evaporated. Residue dissolved in water, basified to pH ~10 using 2N NaOH solution before extracting with Et_2O. Organic layer was then extracted with 2N HCl solution. Acid layer was then basified using 2N NaOH solution before extracting with Et_2O x 3. Combined extracts were dried ($MgSO_4$). Filtered. Evaporated under reduced pressure to afford the title compound as a colurless oil in a 68% yield.
MS (API+): m/z 250.1 (MH+: 100%) @ retention time 1.88 min
$[\alpha]_D$ = + 103°, where l = 1cm, c = 0.5 in DCM

Description 47: (3*R*)-4-(phenylmethyl)-3-morpholinecarboxylic acid (D47)



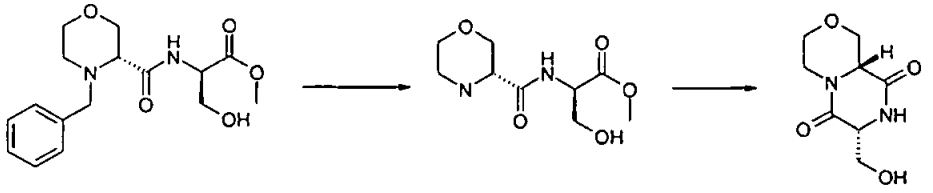
Ethyl (3*R*)-4-(phenylmethyl)-3-morpholinecarboxylate (D46, 2.33g, 9.36mmol) was dissolved in a mixture of THF/EtOH/H_2O (1:1:1 45mL) before treating with Lithium Hydroxide monohydrate (0.432g, 10.29mmol) and heating at 50°C overnight. Reaction not finished. Added more Lithium Hydroxide monohydrate (0.200g, 4.76mmol) and left heating for a further 24 hours. Added more Lithium Hydroxide (0.100g, 2.38mmol) and heated for a further 6 hours. Added more Lithium Hydroxide (0.100g, 2.38mmol) and heated for a further 16 hours.
Cooled to R.T.. Reaction neutralised using 2N HCl solution. Solvent evaporated. Residue partitioned between DCM and Water. Aqueous layer extracted with 10% MeOH/DCM x5. Combined extracts dried ($MgSO_4$). Filtered. Solvent evaporated under reduced pressure to afford the title compound as a white foam in a 94% yield.
MS (API+): m/z 222.1 (MH+; 100%) @ retention time 0.96 min
$[\alpha]_D$ = + 73°, where l = 1cm, c = 0.5 in MeOH

Description 48: Methyl *N*-{[(3*R*)-4-(phenylmethyl)-3-morpholinyl]carbonyl}-D-serinate (D48)



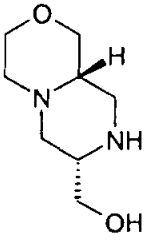
(3*R*)-4-(phenylmethyl)-3-morpholinecarboxylic acid (D47, 1.93g, 8.73mmol) was dissolved in dry DCM (20mL) with a little DMF (2mL). To it was added TBTU (3.62g, 11.27mmol) followed by DIPEA (3.02mL, 17.29mmol) and stirred for 40 minutes at R.T., under argon before adding a solution of D-Ser-Methylester hydrochloride (2.70g, 17.37mmol), and DIPEA (3.02mL, 17.29mmol) in dry DCM (15mL). The resulting mixture was stirred for 45minutes before being allowed to stand overnight. Diluted with DCM (60mL), washed with sat $NaHCO_3$ solution (2 x 60mL). Dried (Na_2SO_4). Filtered. Solvent evaporated under reduced pressure to afford an orange oil. Used crude in the next step.
MS (API+): m/z 323.1 (MH+; 100%) @ retention time 1.17 min
$[\alpha]_D$ = + 11.8 ° , where l = 1cm, c =0.5 in DCM

Description 49: (7*S*,9a*S*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D49)



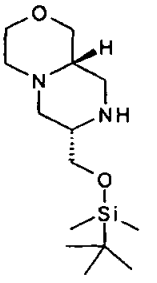
Methyl *N*-{[(3*R*)-4-(phenylmethyl)-3-morpholinyl]carbonyl}-D-serinate (D48, 3.72g, 11.55mmol) was dissolved in EtOH (50mL), treated with 10% Pd on C (450mg) then placed under an atmosphere of hydrogen over the weekend. Left stirring for further 6 hours. Added 10% Pd on C (200mg) and left under an atmosphere of hydrogen overnight. Catalyst removed by filtration through kieselguhr washed with acid, washing well with EtOH. Solvent removed under reduced pressure to afford a colourless oil. Oil dissolved in dry MeOH (15mL) and heated at 50°C overnight. Left heating for a further 3 hours before cooling to R.T.. Solvent removed under reduced pressure. Residue triturated with DCM to afford the title compound as an off white solid in 35% yield over the 2 steps.
MS (ELSD+) : 201.1 (MH+; 100%) @ retention time 0.49 min
$[\alpha]_D$ = + 37.6 °, where l = 1cm, c = 0.5 in MeOH

Description 50: (7*S*,9a*S*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D50)



(7*S*,9a*S*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D49, 800mg, 4mmol) was suspended in dry THF (20mL), before being treated with 1M borane THF complex solution (40mL) and heating at reflux for 17 hours. Cooled to R.T., MeOH (8mL) added dropwise followed by c.HCl solution (3.2mL). The resulting mixture was heated at 70°C for 2 hours. Cooled to R.T., solvent evaporated under reduced pressure. Residue placed on a 10g SCX column in MeOH with some water. Column washed with MeOH (3x 25mL) before eluting the compound with NH_3 in MeOH (4 x 25mL). Solvent evaporated under reduced pressure to afford the title compound as a colourless oil in a quantitative yield.
MS (ELSD+): m/z 173.1 (MH+; 100%) @ retention time 0.31 min
$[\alpha]_D$ = + 3.6° , where l = 1cm, c = 0.5 in MeOH

Description 51: (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D51)



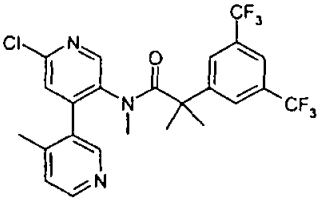
(7*S*,9a*S*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D50, 680mg, 3.95mmol) was almost dissolved in dry DCM (12mL) before adding Et3N (1.10mL, 7.90mmol), followed by TBDMS-Chloride (894mg, 5.93mmol). The resulting reaction mixture was stirred over the weekend at R.T., under argon. Left stirring for 2 more hours.

Diluted with DCM, washed with sat $NaHCO_3$ solution (2 x 20mL). Dried (MgSO4). Filtered. Solvent evaporated. Residue purified on a 25 + M horizon column eluting with 10% EtOAc/Pet Ether to EtOAc to 10% MeOH/EtOAc. Solvent evaporated under reduced pressure to afford the title compound as a pale yellow oil in a 62% yield.

1H NMR (400MHz; DMSO-d6) δ 3.77-3.63 (3H, m), 3.50- 3.40 (2H, m), 2.98 (1H, t), 2.71 (1H, br m), 2.61 (1H, dd), 2.42-2.28 (4H, m), 2.14- 2.05 (2H, m), 1.96 (1H, m), 0.83 (9H, s), 0.01 (6H, s)

$[\alpha]_D$ = + 4.4° , where l = 1cm, c = 0.5 in DCM

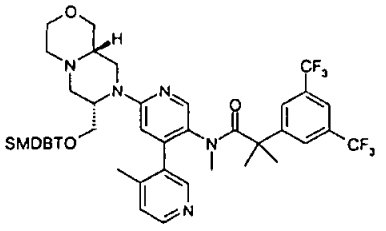
Description 52: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-(6'-chloro-4-methyl-3,4'-bipyridin-3'-yl)-*N*,2-dimethylpropanamide (D52)



2-[3,5-bis(trifluoromethyl)phenyl]-*N*-(6-chloro-4-iodo-3-pyridinyl)-*N*,2-dimethylpropanamide (400mg, 0.726mmol), 4-methylpyridine-3 boronic acid (130mg, 0.944mmol), sodium carbonate (0.8mL, 2M), tetrakistriphenylphosphine palladium (7.8mg, 0.00726mmol) was added in dioxane (4mL) and stirred under argon before heating in the microwave at 110°C for 30 minutes., added more 4-methylpyridine-3 boronic acid (67.5mg, 0.49mmol) and tetrakistriphenylphosphinepalladium (7.8mg, 0.00726mmol) and heated at 110°C for 30 minutes. therefore added more 4-methylpyridine-3 boronic acid (51mg, 037mmol), tetrakistriphenylphosphinepalladium (7.8mg, 0.00726mmol) and heated under microwave conditions at 110°C for 30minutes., therefore added 4-methylpyridine-3 boronic acid (47mg, 0.34mmol),

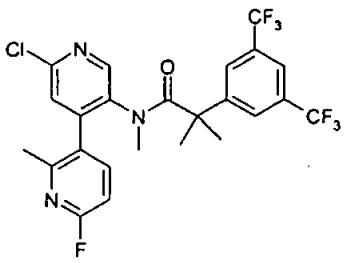
tetrakistriphenylphosphinepalladium (7.8mg, 0.00726mmol) and heated at 110°C for 30 minutes.. Residue partitioned between EtOAc and Brine. Aqueous layer was extracted with EtOAc x3. Combined extracts were dried and solvent evaporated. Residue purified on a 12 +M horizon column eluting with Pet Ether to 1:1 EtOAc: Pet Ether. Unable to isolate clean fractions. Sample sent to be purified by Mass Directed Auto-Prep (MDAP) chromatography, white solid didn't dissolve was found to be desired material. This was combined with product isolated from the MDAP to afford the title compound as a white solid in an 83% yield.
MS (API+): m/z 516.1 (MH+; 100%)

Description 53: 2-[3,5-bis(trifluoromethyl)phenyl]-N-{6'-[(7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-4-methyl-3,4'-bipyridin-3'-yl}-N,2-dimethylpropanamide (D53)



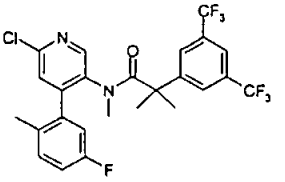
The 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-(6'-chloro-4-methyl-3,4'-bipyridin-3'-yl)-*N*,2-dimethylpropanamide (D52, 77mg, 0.15mmol), (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D51, 51.5mg, 0.18mmol), sodium t-Butoxide (18mg, 0.19mmol) were degassed together in dry toluene(1.5mL) for 5 mins before adding Bis(dibenzyleneacetone) Palladium (9mg, 0.015mmol) and 2-Dicyclohexylphosphino-2'-(N'N'-dimethylamino)biphenyl (15mg, 0.038mmol) and heating under microwave conditions at 130°C for 30mins. Diluted with EtOAC, washed with sat. $NaHCO_3$ x1, brine x1, dried (MgSO4). Filtered. Solvent evaporated. Residue purified eluting with Pent to EtOAc. No Fractions isolated clean. Mixed fractions combined, solvent evaporated and residue re-purified on a 2g SCX column, washing with MeOH (2x10mL) before eluting the compound off with NH3 in MeOH (3x10mL). Solvent evaporated under reduced pressure to afford a gummy solid (86mg).
MS (API+: 766.4 (MH+;100%) + 652.2 (MH+; -TBDMS ; 20%)
Crude product was used directly without further purification.

Description 54: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-(6'-chloro-6-fluoro-2-methyl-3,4'-bipyridin-3'-yl)-*N*,2-dimethylpropanamide (D54)



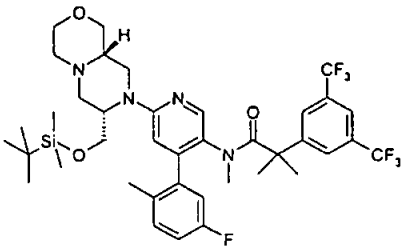
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-(6-chloro-4-iodo-3-pyridinyl)-*N*,2-dimethylpropanamide (200mg, 0.363mmol), 2-fluoro-6-methylpiperidine-5 boronic acid (73mg, 0.472mmol), sodium carbonate solution (0.4mL, 2M), tetrakistriphenylphosphinepalladium (4mg, 0.00363mmol) in dioxan (2mL) were heated together in the microwave at 110°C for 30 minutes. The mixture was partitioned between EtOAc and sat $NaHCO_3$ solution. Aqueous layer extracted with EtOAc x3. Combined extracts dried and evaporated. Residue purified on a 12+M horizon column eluting with Pet Et_2O to 60% EtOAc/Pet Et_2O. Solvent evaporated under reduced pressure to afford the title compound in quantative yield.
MS (API+): m/z 534.2 (MH+; 100%)

Description 55: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(5-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D55)



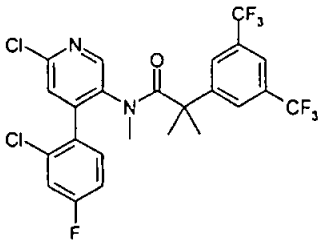
2-[3,5-bis(trifluoromethyl)phenyl]-N-(6-chloro-4-iodo-3-pyridinyl)-N,2-dimethylpropanamide (200mg, 0.363mmol), 2-methyl-5-fluorobenzene boronic acid (73mg, 0.472mmol), sodium carbonate (0.4mL, 2M solution), tetrakistriphenylphosphinepalladium (4mg, 0.00363mmol) in dioxan were heated together in the microwave at 110°C for 30 minutes. The mixture was partitioned between EtOAc and Brine. The Aqueous layer was extracted with EtOAc x3. The combined extracts were dried and evaporated. The residue was purified on a 12+M column eluting with Pet Et_2O to 60% EtOAc/ Pet Et_2O to afford the title compound in a 27% yield.
MS (API+): m/z 533.1 (MH+; 100%)

Description 56: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(5-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D56)



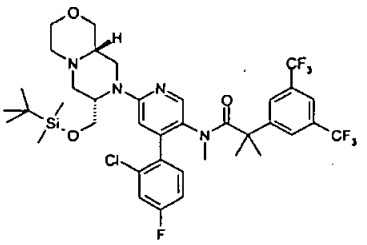
2-[3,5-bis(trifluoromethyl)phenyl]-N-[6-chloro-4-(5-fluoro-2-methylphenyl)-3-pyridinyl]-N,2-dimethylpropanamide (D55, 50mg, 0.094mmol), (7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-c][1,4]oxazine (D51, 34mg, 0.116mmol) were dissolved in toluene (1.5mL). Bis tritertbutylphosphine palladium (12.5mg, 0.0244mmol), followed by hexadecyltrimethylammoium chloride (20μL, 25% aq sol), and finally sodium hydroxide solution (0.11mL, 50% aq sol) were added. The mixture was degassed for 5 minutes before heating at 90°C for 2 hours. Reaction cooled to R.T., diluted with EtOAc, washed with sat $NaHCO_3$ solution, dried ($MgSO_4$). Filtered. Solvent evaporated to afford a yellow sticky solid. Used crude in the next step.
MS (API+): 783.4 (MH+; 60%)

Description 57: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-chloro-4-fluorophenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D57)



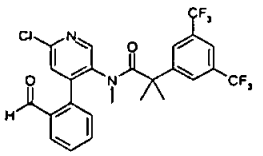
2-[3,5-bis(trifluoromethyl)phenyl]-N-(6-chloro-4-iodo-3-pyridinyl)-N,2-dimethylpropanamide (200mg, 0.363mmol), 2-chloro-4-fluorobenzene boronic acid (82mg, 0.472mmol), sodium carbonate (0.4mL, 2M solution), tetrakistriphenylphosphinepalladium (4mg, 0.00363mmol) in dioxan (2mL) were heated together in the microwave at 110°C for 30 minutes. The mixture was partitioned between EtOAc and Brine. The Aqueous layer was extracted with EtOAc x3. The combined extracts were dried and evaporated. The residue was purified on a 25+M column eluting with 0- 50% EtOAc/ Pet Et_2O. Impurities still seen. Sent to MDAP for purification to afford the title compound in a 96% yield.
MS (API+): m/z 553.1 (MH+; 100%)

Description 58: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(2-chloro-4-fluorophenyl)-6-[(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (D58)



2-[3,5-bis(trifluoromethyl)phenyl]-N-[6-chloro-4-(2-chloro-4-fluorophenyl)-3-pyridinyl]-N,2-dimethylpropanamide (D57,60mg, 0.11mmol),), (7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-c][1,4]oxazine (D51, 37mg, 0.13mmol), sodium t-Butoxide (13mg, 00.1375mmol) were degassed together in toluene (1.2mL) for 10minutes before adding bis(dibenzyleneacetone) palladium (6mg, 0.011mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (11mg, 0.0275mmol) and heating at 100°C for 30 minutes under microwave conditions. Added more bis(dibenzyleneacetone) palladium (6mg, 0.011mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (11mg, 0.0275mmol) and heated for a further 30 minutes at 100°C under microwave conditions. Diluted with EtOAc, washed with sat $NaHCO_3$ solution x1, brine x1, dried (MgSO4). Filtered. Solvent evaporated under reduced pressure. Residue purified eluting with 0- 100% EtOAc/Pent. Solvent evaporated to afford a brown gum of the title compound in 25% yield.
MS (API+): m/z 803.4 (MH+; 40%)

Description 59: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-formylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D59)

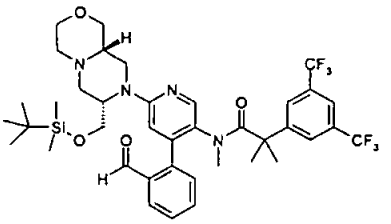


2-[3,5-bis(trifluoromethyl)phenyl]-N-(6-chloro-4-iodo-3-pyridinyl)-N,2-dimethylpropanamide (200mg, 0.363mmol), benzaldehyde-2-boronic acid (71mg, 0.472mmol), sodium carbonate (0.4mL, 2M solution), tetrakistriphenylphosphinepalladium (4mg, 0.00363mmol) in dioxan (2mL) were heated together in the microwave at 110°C for 30 minutes. The mixture was partitioned between EtOAc and Brine. The Aqueous layer was extracted with EtOAc x3. The combined extracts were dried and evaporated. The residue was purified on

80

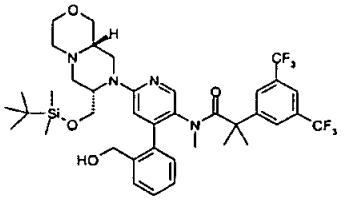
a 25+M column eluting with 0- 50% EtOAc/ Pet Et_2O to afford the title compound as a yellow solid in 55% yield.
MS (API+): m/z 529.1 (MH+; 100%)

Description 60: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(2-formylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D60)



2-[3,5-bis(trifluoromethyl)phenyl]-N-[6-chloro-4-(2-formylphenyl)-3-pyridinyl]-N,2-dimethylpropanamide (D59, 106mg, 0.201mmol),), (7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-c][1,4]oxazine (D51, 72mg, 0.251mmol) were dissolved in toluene (2mL). Bis tritertbutylphosphine palladium (27mg, 0.052mmol), followed by hexadecyltrimethylammoium chloride (30µL, 25% aq sol), and finally sodium hydroxide solution (0.25mL, 50% aq sol) were added. The mixture was degassed for 5 minutes before heating at 90°C for 2 hours. Reaction cooled to R.T., diluted with EtOAc, washed with sat NaHCO3 solution, dried (MgSO4). Filtered. Solvent evaporated. Residue purified eluting with 0 – 50% EtOAc /Pent. Solvent evaporated under reduced pressure to afford a pale yellow solid in 18% yield.
MS (API+): m/z 779.4 (MH+; 100%).

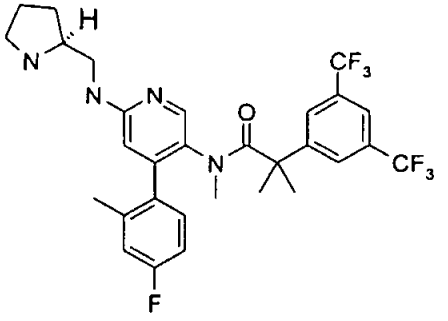
Description 61: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6-[(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-[2-(hydroxymethyl)phenyl]-3-pyridinyl}-*N*,2-dimethylpropanamide (D61)



2-[3,5-bis(trifluoromethyl)phenyl]-N-[6-[(7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-4-(2-formylphenyl)-3-pyridinyl]-N,2-dimethylpropanamide (D60, 27.7mg, 0.0356mmol) was suspended in dry THF (1.5mL) before adding sodium

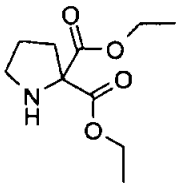
borohydride (3mg, 0.078mmol) and stirring for 1 hour. Added more sodium borohydride (3mg, 0.078mmol) and left stirring for a further 1 and ½ hours. Reaction quenched with water, diluted with EtOAc. Organic layer washed with water, dried ($MgSO_4$). Filtered. Solvent evaporated to afford the title compound as an off white solid in 89% yield. Used crude in the next step.
MS (API+): m/z 781.4 (MH+; 100%).

Description 62: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-(4-(4-fluoro-2-methylphenyl)-6-{[(2*S*)-2-pyrrolidinylmethyl]amino}-3-pyridinyl)-*N*,2-dimethylpropanamide (D62)



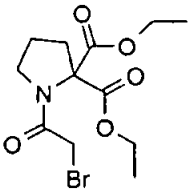
A suspension of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (1.5 g, 2.81 mmol) 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-pyrrolidinecarboxylate (*N*-Boc prolinamine) (1.41 g, 7.025 mmol) and potassium carbonate (777 mg, 5.62 mmol) in 6 mL of DMSO was heated for 18 h at 150°C (temperature detected 138°C). A HPLC/MS check showed a 50% conversion with partial loss of the Boc protecting group. The reaction was heated under microwave irradiation to 160°C for 1h and to 180°C for two cycles of 1h and 1.5 h, respectively. The suspension was diluted with dichloromethane and extracted with sat. $NaHCO_3$ and the organics were dried (Na_2SO_4) and the solution was loaded on a SCX cartridge, washed with dichloromethane (100 mL) and methanol (200 mL, this wash allowed the recovery of the unreacted chloropyridine) and eluted with 2M NH_3 in MeOH. The crude thus obtained, which contained both the Boc-protected and unprotected compounds, was purified by flash chromatography (silica, cyclohexane: EtOAc 80:20 to EtOAc). Isolated 350 mg of Boc-protected amine and 410 mg of the title compound. This last compound was purified further by a boc-protection, flash chromatography, TFA deprotection and SCX isolation procedure. Final yield: 165 mg.
O.A.HPLC, peak @ 5.20 min, >99% purity (UV).

Description 63: diethyl 2,2-pyrrolidinedicarboxylate (D63)



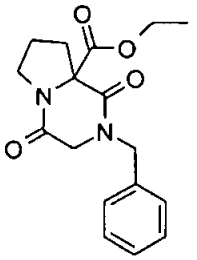
To a solution of sodium ethoxide (5.14 g) in absolute ethanol (75 mL) at 0°C under a nitrogen atmosphere, a solution of diethyl aminomalonate (hydrochloride salt, 8 g) in absolute ethanol (75 mL) was slowly added. A yellow suspension was obtained at the end of the addition. 1, 3-dibromo propane (7.7 mL) was then added and the resulting mixture was stirred at reflux temperature for 5 hours. The mixture was allowed to cool down to rt, then ethanol was removed in vacuo to give a yellow solid. This was dissolved in HCl (1M solution, 20 mL) and then washed with ethyl ether (2 x 50 mL). Phases were separated and the aqueous phase was brought to pH = 9 by adding NaOH (1M solution). It was then extracted with ethyl ether (3 x 50mL) and washed with brine (20 mL). The organic phase was dried and concentrated *in vacuo* to give the desired compound (2.35 g) as yellow oil.
MS (ES/+) m/z=216 $[M+H]^+$.

Description 64: diethyl 1-(bromoacetyl)-2,2-pyrrolidinedicarboxylate (D64)



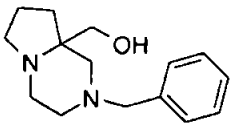
To a solution of diethyl 2,2-pyrrolidinedicarboxylate (D63, 900 mg) in dichloromethane (9 mL) at 0°C, potassium carbonate (0.5M solution, 12.5 mL) and bromoacetyl bromide (0.55mL) were added. The resulting mixture was stirred at 0°C for 2 hours. The mixture was then diluted with water and then allowed to reach r.t. Ethyl acetate (15 mL) was added and phases were separated. The aqueous phase was then extracted with ethyl acetate (2 x 10mL) and washed with brine (20 mL). The organic phase was dried and concentrated *in vacuo* to give the desired compound (1.06g) as orange oil.
T.l.c.: CH/AcOEt 1:1, Rf=0.47.
UPLC/MS: peak at Rt = 0.63 min with m/z = 336, 338 $[M+H]^+$.

Description 65: ethyl 1,4-dioxo-2-(phenylmethyl)hexahydropyrrolo[1,2-*a*]pyrazine-8a(6*H*)-carboxylate (D65)



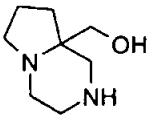
To a solution of diethyl 1-(bromoacetyl)-2,2-pyrrolidinedicarboxylate (D64, 950 mg) in acetonitrile (10 mL) at r.t, benzylamine (340 microL) was added. The resulting mixture was stirred at r.t. for 3.5 hours: the formation of a white solid was observed. The suspension was then filtered over a Gooch funnel. The organic filtrate was diluted with ethyl acetate (15 mL) and washed with water (2 x 10 mL). The organic phase was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (Cycl/EtOAc from 50/50 to 35:65) to give the desired compound (200 mg) as colourless oil.
T.l.c.: CH/AcOEt 7:3, Rf=0.53.
UPLC/MS: peak at Rt = 0.62 min with m/z = 317 $[M+H]^+$.
1H NMR (500 MHz, CHLOROFORM-*d*) d ppm 7.34 (t, 1 H) 7.32 (t, 2 H) 7.23 (dd, 2 H) 4.97 (d, 1 H) 4.25 (d, 1 H) 4.19 - 4.25 (m, 2 H) 4.01 (d, 1 H) 3.74 (d, 1 H) 3.67 - 3.76 (m, 1 H) 3.55 - 3.63 (m, 1 H) 2.71 - 2.80 (m, 1 H) 2.36 - 2.46 (m, 1 H) 1.93 - 2.11 (m, 2 H) 1.21 (t, 3 H).

Description 66: [2-(phenylmethyl)hexahydropyrrolo[1,2-*a*]pyrazin-8a(6*H*)-yl]methanol (D66)



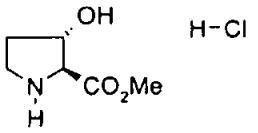
To a solution of ethyl 1,4-dioxo-2-(phenylmethyl)hexahydropyrrolo[1,2-*a*]pyrazine-8a(6*H*)-carboxylate (D65, 450 mg) in anhydrous THF (5 mL) under a Nitrogen atmosphere at 0°C, lithium aluminium hydride (1M in THF, 14 mL) was added dropwise. The resulting mixture was stirred at 0°C for 10 minutes, then allowed to reach rt and stirred at this temperature for 45 minutes. It was then heated at reflux temperature for 3.5 hours and then allowed to cool to r.t. Water (540 microL), NaOH (1M solution, 540microL) and water (1.6 mL) were then added to the solution and the formation of a white precipitate was observed. The suspension was stirred at rt for 30-40 minutes then filtered over a Gooch funnel. The organic filtrate was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (DCM/MeOH from 100/0 to 90:10) to give the desired compound (162 mg) as orange oil.
T.l.c.: DCM/MeOH 9:1, Rf=0.43.
UPLC/MS: peak at Rt = 0.43 min with m/z = 247 $[M+H]^+$.

Description 67: hexahydropyrrolo[1,2-*a*]pyrazin-8a(6*H*)-ylmethanol (D67)



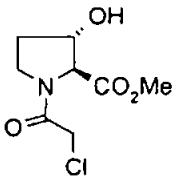
To a solution of [2-(phenylmethyl)hexahydropyrrolo[1,2-*a*]pyrazin-8a(6*H*)-yl]methanol (D66, 180 mg) in anhydrous methanol (5 mL) under a Nitrogen atmosphere at rt, ammonium formate (475 mg) and palladium (10% on carbon, 13 mg) were added. The resulting suspension was heated at reflux temperature for 3.5 hours, then allowed to cool to r.t. and filtered over Celite. The organic extract was dried and concentrated *in vacuo* to give the desired compound (120 mg) as orange waxy solid.
UPLC/MS: peak at Rt = 0.15 min with m/z = 157 $[M+H]^+$.
1H NMR (400 MHz, DMSO-d_6) d ppm 5.09 (br. s., 1 H) 3.61 (d, 1 H) 3.34 (br. s., 1 H) 2.89 - 3.09 (m, 5 H) 2.76 - 2.89 (m, 2 H) 2.72 (d, 1 H) 1.62 - 1.84 (m, 3 H) 1.49 - 1.61 (m, 1 H)

Description 68: methyl (3*S*)-3-hydroxy-L-prolinate hydrochloride (D68)



Hydrogen chloride gas was bubbled through a suspension of *trans*-3-hydroxy-L-proline (1.5 g, 11.4 mmol) in 20 ml of freshly distilled MeOH at 0°C for 30 min. The resulting clear solution was stirred overnight, then concentrated under reduced pressure to afford the title compound as a white solid (1.96 g). Yield 94%.
Reference: U.S. Pat. Appl. 2004 19,063.

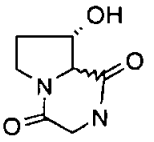
Description 69: methyl (3*S*)-1-(chloroacetyl)-3-hydroxy-L-prolinate (D69)



To a solution of the methyl (3*S*)-3-hydroxy-L-prolinate hydrochloride (D68, 1.8 g, 9.9 mmol) and Et_3N (3 ml, 21.8 mmol) in 10 ml of dry benzene at the temperature of 7-8 °C was added dropwise a solution of chloroacetyl chloride (0.87 ml, 10.9 mmol) in 5 ml of dry benzene. After 24 h at rt, the precipitated was filtered off and washed with

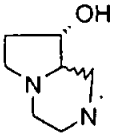
AcOEt. The filtrate was evaporated, and the crude oil was purified by flash chromatography column (Cy/AcOEt 1/4 as eluent). The title compound was isolated as a colourless oil (1.48 g). Yield 67%.
Reference: *Khimiko-Farmatsevticheskii Zhurnal* **1984**, *18*, 1445-8; *Eur. J. Org. Chem.* **2000**, 657.

Description 70: (8*S*)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D70)



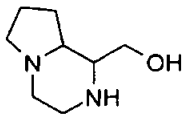
A mixture of methyl (3*S*)-1-(chloroacetyl)-3-hydroxy-L-prolinate (D69, 1.48 g, 6.7 mmol) in 10 ml of MeOH and 60 ml of a saturated solution of NH_3 in MeOH was stirred for 48 h at rt. The solvent was evaporated under reduced pressure, to afford a solid. Analysis indicated this to be the title compound as a pair of diastereoisomers. After a short chromatography column ($CHCl_3$/MeOH 8/2 as eluent) the title compound was isolated as a foamy solid (1g). Yield 88%.
Reference: *Khimiko-Farmatsevticheskii Zhurnal* **1984**, *18*, 1445-8

Description 71: (8*S*)-octahydropyrrolo[1,2-*a*]pyrazin-8-ol (D71)



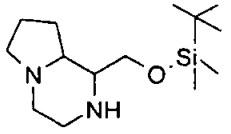
Into a stirred, cooled (0 °C) suspension of $LiAlH_4$ (3.3 g, 88 mmol) in 60 ml of dry THF, was introduced (8*S*)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D70, 750 mg, 4.4 mmol) in small portions. The mixture was then allowed to reach rt and stirred for 48h, after which it was cooled to 0 °C. THF was introduced (70 ml), then successively a saturated solution of Na-K-tartrate (5 ml) and a 20% aqueous NaOH solution (5 ml) were dropped into the flask, under vigorous stirring. The suspension was stirred for 30 min at rt, and filtered. The pale filter cake was washed with 100 ml of $CHCl_3$ and the combined filtrates and washings were evaporated in vacuo to give 500 mg of the title compound. From GC-MS analysis 2 diastereomeric products were still observed. Yield 80%.
1H NMR (500 MHz, DMSO-*d*6) δ ppm 4.01 (s, 1 H) 2.93 (t, 1 H) 2.87 (d, 1 H) 2.80 (d, 1 H) 2.71 (d, 1 H) 2.49 - 2.61 (m, 2 H) 1.89 - 2.06 (m, 2 H) 1.74 - 1.91 (m, 2 H) 1.48 - 1.56 (m, 1 H) 1.34 - 1.42 (m, 1 H)
Reference: *J. Org. Chem.* **1995**, *60*, 3916.

Description 72: *cis*-Octahydropyrrolo[1,2-*a*]pyrazin-1-ylmethanol (D72)



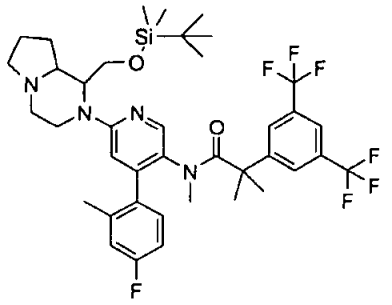
To a solution of *cis*- methyl -3-oxooctahydropyrrolo[1,2-*a*]pyrazine-1-carboxylate (Prepared according literature procedure :Heterocycles, 52(3), 2000)(270 mg) in anhydrous THF (10 mL) under a Nitrogen atmosphere at 0°C, lithium aluminium hydride (1M in THF, 6.8 mL) was added dropwise. The resulting mixture was stirred at 0°C for 1 hour, then allowed to reach rt and stirred at this temperature for 30 minutes. Water (260 microL), NaOH (1M solution, 260 microL) and water (780 microL) were then added to the solution and the formation of a white precipitate was observed. The suspension was filtered over a Gooch funnel. The organic filtrate was dried and concentrated *in vacuo* to give the desired compound (198 mg) as yellow oil.
UPLC/MS: peak at Rt = 0.15 min with m/z = 157 $[M+H]^+$.
1H NMR (500 MHz, CHLOROFORM-*d*) d ppm 3.94 - 4.04 (m, 1 H) 3.75 (dd, 1 H) 3.19 (td, 1 H) 3.07 - 3.15 (m, 1 H) 3.05 (t, 1 H) 2.96 - 3.04 (m, 1 H) 2.78 - 2.90 (m, 2 H) 2.29 - 2.40 (m, 1 H) 2.17 (td, 1 H) 2.02 - 2.15 (m, 1 H) 1.58 - 1.86 (m, 4 H).

Description 73: *cis*-1-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrrolo[1,2-*a*]pyrazine (D73)



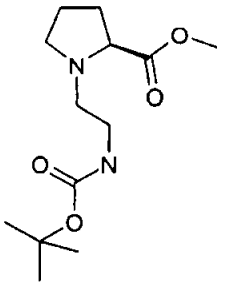
To a solution of *cis*- Octahydropyrrolo[1,2-*a*]pyrazin-1-ylmethanol (D72, 198 mg) in anhydrous DCM (10 mL) under a Nitrogen atmosphere at room temperature, triethylamine (350 microL) and t-butyldimethylsilylchloride (286 mg) were added. The resulting solution was stirred at room temperature overnight then diluted with water (5 mL). The aqueous phase was extracted with DCM (2 x 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (DCM/0.5M NH_3 in MeOH from 100/0 to 90/10) to give the desired compound (195 mg) as yellow oil.
UPLC/MS: peak at Rt = 0.80 min with m/z = 271 $[M+H]^+$.
1H NMR (500 MHz, CHLOROFORM-*d*) d ppm 3.84 (t, 1 H) 3.61 (dd, 1 H) 3.11 - 3.21 (m, 1 H) 2.99 (dd, 2 H) 2.82 - 2.88 (m, 1 H) 2.71 - 2.79 (m, 1 H) 2.41 - 2.50 (m, 1 H) 2.19 - 2.35 (m, 2 H) 1.71 - 1.85 (m, 1 H) 1.94 (br. s., 1 H) 1.53 - 1.73 (m, 3 H) 0.90 (s, 9 H) 0.07 (s, 6 H)

Description 74: *cis*- 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[1-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D74)



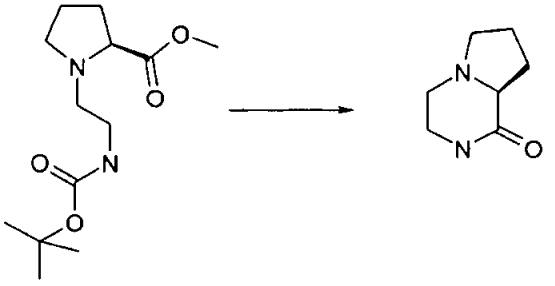
To a solution of *cis*-1-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrrolo[1,2-*a*]pyrazine (D73, 50 mg) in dry toluene (0.5 mL), a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (75 mg) in dry toluene (0.5 mL) was added at rt. Hexadecyltrimethylammonium chloride (25% aqueous solution, 132 microL), bis(tri-tert-butyl phosphine) palladium (19 mg) and NaOH (50% aqueous solution, 245 microL) were added. The resulting mixture was degassed by two freeze-thaw cycles and allowed to reach rt under a nitrogen atmosphere. The mixture was then heated at 90°C for 5 hours. The mixture was allowed to cool down to rt, diluted with ethyl acetate (1 mL) and washed with a saturated solution of $NaHCO_3$ (1 mL). The aqueous phase was extracted with ethyl acetate (3 x 2.5 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (Cycl/EtOAc 1:1) to give the desired compound (10.5 mg) as yellow oil.
T.l.c.: Cycl/EtOAc 1:1, Rf=0.49.
UPLC/MS: peak at Rt = 0.87 min with m/z = 767 $[M+H]^+$.

Description 75: methyl 1-[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]-L-prolinate (D75)



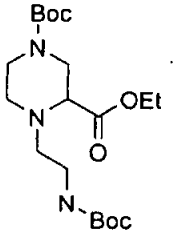
To a solution of methyl L-prolinate (892 mg, 6.93 mmol) in dichloroethane (20 ml) was added at r.t. 1,1-dimethylethyl (2-oxoethyl)carbamate (1 g, 6.3 mmol) and the reaction mixture was stirred for 30 min. Sodium triacetoxyborohydride (2.34 g, 12.6 mmol) was added and the reaction mixture was stirred for 3 hrs.
The title compound (1 g) was isolated after purification via SCX.
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 5.11 - 5.49 (m, 1 H) 3.59 - 3.88 (m, 4 H) 3.05 - 3.41 (m, 4 H) 2.71 - 2.90 (m, 1 H) 2.54 - 2.73 (m, 1 H) 2.34 - 2.51 (m, 1 H) 2.03 - 2.30 (m, 1 H) 1.27 - 2.04 (m, 11 H)

Description 76: (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (D76)



To a solution of methyl 1-[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]-L-prolinate (D75,1 g) in dichloromethane (20 ml) was added at r.t. TFA (5 ml) and the reaction mixture was stirred for 1 hr. The mixture was diluted with MeOH and it was filtered trough SCX cartridge. The fractions eluted with methanolic ammonia were evaporated *in vacuo* keeping the bath temperature at 40°C.
The crude was purified by chromatography (silica cartridge, CH_2Cl_2:MeOH 95:5) to give the title compound (420 mg).
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 5.86 - 6.38 (m, 1 H) 3.47 - 3.70 (m, 1 H) 3.24 - 3.47 (m, 2 H) 2.87 - 3.13 (m, 3 H) 2.65 - 2.87 (m, 1 H) 2.14 - 2.37 (m, 1 H) 1.69 - 2.10 (m, 3 H)

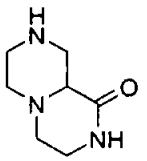
Description 77: 1-(1,1-dimethylethyl) 3-ethyl 4-[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]-1,3-piperazinedicarboxylate (D77)



To a solution of 1-(1,1-dimethylethyl) 3-ethyl 1,3-piperazinedicarboxylate [EP1486498, 2004] (2.023 g, 8.28 mmol) in 10 mL of dichloroethane was added a

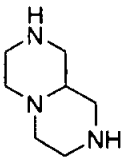
solution of *N*-boc-2-aminoacetaldehyde (1.87 g, 12.42 mmol) in 20 mL of dichloroethane. The solution was stirred at room temperature and under nitrogen atmosphere for 30 min. Sodium triacetoxyborohydride (3.32 g, 16.56 mmol) was then added and the reaction kept at room temperature overnight. The product was isolated on a SCX cartridge. 2.492 g.
LC/MS: peak at 2.16 min, m/z= 402 (M+1).

Description 78 :hexahydro-2*H*-pyrazino[1,2-*a*]pyrazin-1(6*H*)-one (D78)



To a solution of 1-(1,1-dimethylethyl) 3-ethyl 4-[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]-1,3-piperazinedicarboxylate (D77, 2.492 g, 6.21 mmol) in dichloromethane (30 mL) kept at 0°C was added TFA (10 mL) dropwise. The solution was kept at 0°C for 2 h, and then at room temperature for 6 h. The deprotected product was isolated by SCX and the resulting solution was evaporated at 50°C to induce cyclization. The target product was purified by reverse phase chromatography (Oasis HLB 6g x 4 columns, eluted with water), obtaining 372 mg of the title compound.
1H NMR (500 MHz, DMSO-d_6) δ ppm 7.65 (br. s., 1 H) 3.20 - 3.30 (m, 2 H) 2.98 - 3.07 (m, 1 H) 2.84 (d, 1 H) 2.72 - 2.80 (m, 2 H) 2.68 (dt, 1 H) 2.49 - 2.52 (m, 1 H) 2.40 - 2.46 (m, 1 H) 2.35 (dt, 1 H) 2.12 (dt, 1 H)

Description 79: octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D79)

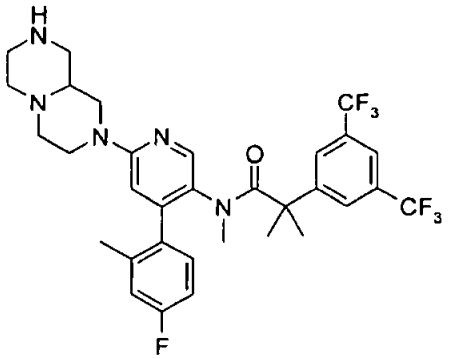


To a suspension of hexahydro-2*H*-pyrazino[1,2-*a*]pyrazin-1(6*H*)-one (D78, 339 mg, 2.184 mmol) in 3.5 mL of THF kept at 0°C were added dropwise 21.84 mL of a 1M borane-THF solution. The reaction was kept at 75°C under nitrogen atmosphere for 3h, then quenched by slow addition MeOH at 0°C. After 30 min at room temperature, 5 mL of a 37% HCl aqueous solution diluted in 10 mL of MeOH were added and the resulting solution was heated to 50°C for 2.5 h. The solvent was removed and the residue purified by SCX, leaving 251 mg of the title compound.
MS (direct): m/z= 142 (M+1)
1H NMR (500 MHz, DMSO-d_6) δ ppm 2.44 - 2.77 (m, 8 H) 2.17 (t, 2 H) 1.97 (dt, 2 H) 1.73 - 1.84 (m, 1 H)

90

Description 80: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide

(D80)

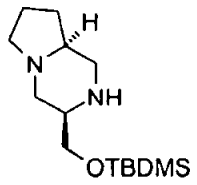


To a solution of octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D79, 197 mg, 1.395 mmol) in 6 mL of DMSO was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (372 mg, 0.698 mmol) and potassium carbonate (289 mg, 2.09 mmol) and the reaction was heated at 130°C for 22 h. The product was isolated by SCX, and the obtained crude (451 mg) was used in the following reactions without further purification.

MS(direct): m/z= 638 (M+1).

Description 81: (3*R*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrrolo[1,2-*a*]pyrazine

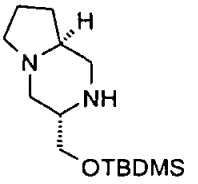
(D81)



To a solution of (3*R*,8a*S*)-octahydropyrrolo[1,2-*a*]pyrazin-3-ylmethanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005), 220 mg, 1.41 mmol) in 8 mL of dichloromethane was added triethylamine (262 µL, 2.82 mmol) and a solution of tert-butyldimetlylsilyl chloride (170 mg, 1.7 mmol) in dichloromethane (1 mL) and the solution was stirred at room temperature for 3h. Additional tert-butyldimetlylsilyl chloride (113 mg, 1.1 mmol) was added, and the solution left at room temperature overnight. More triethylamine (261 µL, 2.82 mmol) and tert-butyldimetlylsilyl chloride (71 mg, 0.69 mmol) was added again, and the reaction left at room temperature for 5 h. The reaction was diluted with dichloromethane and extracted with sat. $NaHCO_3$

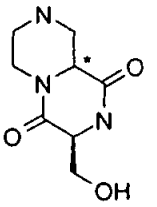
and brine. The product was isolated by flash chromatography (dichloromethane to dichloromethane: 0.5 M NH_3 in MeOH 9:1), obtaining 259 mg of the title compound. 1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.89 (t, 1 H) 3.60 (dd, 1 H) 3.01 - 3.10 (m, 3 H) 2.95 (dt, 1 H) 2.79 (dd, 1 H) 2.75 (dd, 1 H) 2.49 (dd, 1 H) 2.23 - 2.40 (m, 2 H) 1.66 - 1.89 (m, 3 H) 1.43 - 1.57 (m, 1 H) 0.90 (s, 9 H) 0.08 (s, 6 H) LC/MS (check at 5h reaction): peak @0.49 min, m/z= 271 (M+1).

Description 82: (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrrolo[1,2-*a*]pyrazine (D82)



To a solution of (3*RS*,8a*S*)-octahydropyrrolo[1,2-*a*]pyrazin-3-ylmethanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005) (531.5 mg, 3.39 mmol) in 20 mL of dichloromethane was added triethylamine (1.423 mL, 10.17 mmol) and tert-butyldimetlylsilyl chloride (1.026 g, 6.78 mmol). The solution was stirred at room temperature for 2 days. The reaction was diluted with dichloromethane and extracted with sat. $NaHCO_3$ and brine. The product was isolated by flash chromatography (dichloromethane to dichloromethane: MeOH 99:1 to 90:10), obtaining 157 mg of the title compound.
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.60 - 3.70 (m, 1 H) 3.47 - 3.59 (m, 1 H) 2.90 - 3.28 (m, 3 H) 2.50 - 2.73 (m, 1 H) 2.09 - 2.30 (m, 1 H) 1.79 - 2.09 (m, 2 H) 1.37 - 1.80 (m, 5 H) 0.87 - 0.97 (s, 9 H) 0.03 - 0.13 (s, 6 H).

Description 83 and 84: (3*S*,*9aS or 9aR*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D83 - Diatereoisomer 1) and (*3S,9aR or 9aS*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D84-Diastereoisomer 2)



To a solution of the *N,N'*-di-boc-piperazine-2-carboxylic acid (2 g) in 60 mL of dichloromethane was added HOBt (817 mg) and EDC (1.74 g). The reaction was stirred for 30 min. In the meantime, a solution of L-serine methyl ester hydrochloride (1.413 g, n mmol) and diisopropylethylamine (1.62 mL) in 20 mL of dichloromethane

was prepared and finally added to the reaction mixture. The reaction was left stirring at room temperature overnight. UPLC-MS analysis showed the expected product (peak at 0.67 min, m/z = 432 (M+1), 376 (M - *t*-Bu), 320 (M – Boc +1)). The reaction was diluted with dichloromethane and extracted with sat. $NaHCO_3$, dried (Na_2SO_4), and the solvent removed. The crude (2.75 g) was taken to the next step without further purification.

It was dissolved in 30 mL of dichloromethane and treated with 10 mL of TFA, added at 0°C. The reaction was stirred at room temperature for 1.5 h. It was checked by UPLC/MS, which showed the expected deprotection product at 0.20 min, m/z = 232 (M+1). The crude was purified by SCX. The basic fractions were stirred at 50°C and evaporated. The solid thus obtained was suspended in 5 mL of MeOH and filtered to give the title compound (D83- Diastereoisomer 1) as a white solid 333 mg.

D 83:

1H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (s, 1 H) 5.07 (t, 1 H) 4.15 (dd, 1 H) 3.67 - 3.77 (m, 3 H) 3.40 - 3.49 (m, 1 H) 3.20 (dd, 1 H) 2.82 (dd, 1 H) 2.45 - 2.52 (m, 1 H) 2.31 - 2.42 (m, 2 H)

UPLC/MS: Peak @ 0.16 min, m/z= 200 (M+1).

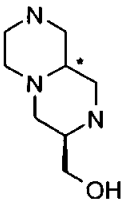
The solution was concentrated to give a second solid (976 mg) as a mixture of title compounds: (Mixture of D83-Diastereoisomer 1 and D84- Diastereoisomer 2).

D83+D84:

1H NMR (400 MHz, DMSO-d_6) δ ppm 7.93 – 8.08 (m, 1 H) 5.06 – 5.19 (m, 1 H) 4.14 – 4.33 (m, 1 H) 3.67 - 3.77 (m, 3 H) 3.40 - 3.49 (m, 1 H) 3.11- 3.23 (m, 1 H) 2.75 – 2.90 (m, 1 H) 2.45 - 2.52 (m, 1 H) 2.31 - 2.42 (m, 2 H).

UPLC/MS: Peak @ 0.16 min, m/z= 200 (M+1).

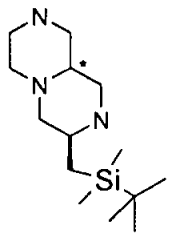
Description 85: (3*R*,9a*S or 9aR*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol (D85 – Diastereoisomer 1)



To a flask containing (3*S*,*9aS or 9aR*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D83, 217 mg) was added 1M BH_3-THF solution (10.9 mL) and the reaction was brought to reflux (80°C) overnight. The reaction flask was cooled to 0°C and treated with 20 mL of MeOH and conc. HCl (2.5 mL). The resulting solution was heated to 60°C for 4 h. The reaction was checked by direct MS (m/z= 172 (M+1), 184 (M+BH_3)). The reaction mixture was purified by SCX, obtaining 174 mg of the title compound.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.39 - 4.63 (m, 1 H) 3.17 - 3.26 (m, 2 H) 2.56 - 2.79 (m, 6 H) 2.14 - 2.31 (m, 2 H) 1.92 - 2.04 (m, 1 H) 1.72 - 1.85 (m, 1 H) 1.66 (t, 1 H).

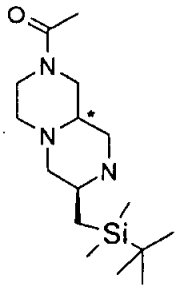
Description 86: (3*R*,9a*S or 9aR*)-3-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D86 – Diasteroisomer 1)



The starting (3*R*,9a*S or 9aR*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol (D85, 173 mg) was dissolved in 6 mL of dichloromethane and treated with Et_3N (420 µL) and TDBMSCl (305 mg). The reaction was stirred at room temperature for 3 days. More TDBMSCl (144 mg, n mmol) was added and the reaction stirred again overnight. It was checked by UPLC/MS, which showed conversion to product: peak at 0.47 min, m/z = 286 (M+1). The crude was purified by flash chromatography (silica, CH_2Cl_2 to CH_2Cl_2 : (0.5 M NH_3 in MeOH) 90:10), to give 218 mg of the expected product.

1H NMR (400 MHz, DMSO-d_6) δ ppm 3.34 - 3.53 (m, 2 H) 2.92 - 3.12 (m, 2 H) 2.60 - 2.92 (m, 6 H) 2.26 - 2.39 (m, 1 H) 2.11 - 2.27 (m, 1 H) 1.98 - 2.11 (m, 1 H) 1.70 - 1.83 (m, 1 H) 1.23 (t, 1 H) 0.80 - 0.92 (m, 9 H) -0.02 - 0.09 (m, 6 H).

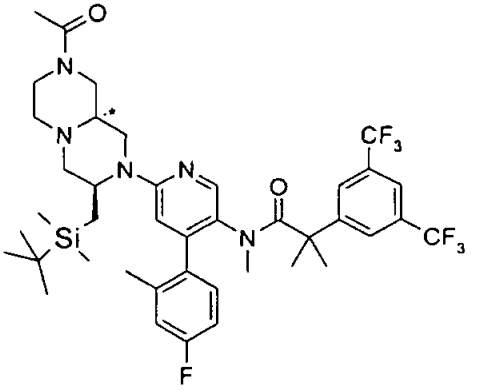
Description 87: (7*R*,9a*R or 9aS*)-2-acetyl-7-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D87 – Diastereoisomer 1)



To a solution of the (3*R*,9a*S or 9aR*)-3-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D86, 217 mg) in 9 mL of dichloromethane was added triethylamine (212 µL) and it was brought to – 10 °C. A solution of acetyl chloride (54 µL) in 2 mL of dichloromethane was added dropwise. After 15 min the reaction was quenched by addition of MeOH. The crude was purified by flash chromatography (silica, CH_2Cl_2 to CH_2Cl_2 : (0.5 M NH_3 in MeOH) 95:5). The sample thus obtained was dissolved in CH_2Cl_2 and

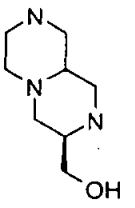
extracted with sat. NaHCO3. The organics were dried and the solvent removed, leading to the title compound (128 mg).
LC/MS: m/z=328 (M+1)
1H NMR (500 MHz, DMSO-d_6) δ ppm 4.25 (dd, 1 H) 3.62 (dd, 1 H) 3.36 - 3.46 (m, 2 H) 2.83 (dd, 1 H) 2.62 - 2.76 (m, 4 H) 2.55 - 2.62 (m, 1 H) 2.26 - 2.33 (m, 1 H) 1.96 (s, 3 H) 1.85 - 1.92 (m, 1 H) 1.80 (t, 1 H) 1.67 (t, 1 H) 0.84 (s, 9 H) 0.01 (s, 6 H).

Description 88: *N*-[6-((3*R*,9a*R or 9aS*)-8-acetyl-3-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D88 – Diastereisomer 1)



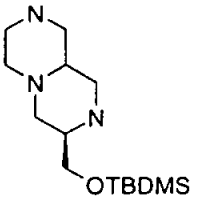
To a solution of (7*R*,9a*R or 9aS*)-2-acetyl-7-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D87, 125 mg, 5.72 mmol) in 1.5 mL of toluene was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (156 mg, n mmol), bis-tri –tert-butylphosphine palladium (30 mg, n mmol), hexadecyltrimetylammonium chloride (19 μL of a 25% aqueous solution) and, at last, sodium hydroxide solution (35 μL of a 50% aqueous solution). The solution was degassed by freeze-pump-thaw cycles, then stirred at 90°C for 3.75 h. It was checked by UPLC/MS, which showed peaks for the expected product at 0.94 min. (m/z = 824 (M+1), 412 (M+2)/2). The solution was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine. The product were isolated by flash chromatography (cyclohexane:EtOAc 50:50 -> 0:100), obtaining 149 mg of the title compound that were brought directly to the next step.

Description 89: (3*R*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol (D89)



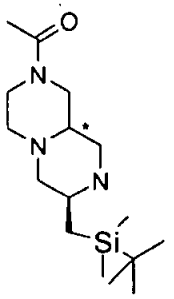
To a flask containing (3*S,9aS or 9aR*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione and (*3S,9aR or 9aS*)-3-(hydroxymethyl)tetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D83, Diastereoisomer 1 plus D84,Diastereoisomer 2, 976 mg, 4.9 mmol) was added 1M BH_3-THF solution (49 mL) under nitrogen and the reaction was brought to reflux (80°C) overnight. The reaction flask was cooled to 0°C and treated with 25 mL of MeOH. Conc. HCl was added and the resulting solution was heated to 60°C for 5 h. The reaction was checked by direct MS (m/z= 184 ($M+BH_3$)). The reaction mixture was purified by SCX, obtaining 528 mg of product.

Description 90: (3*R*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D90)



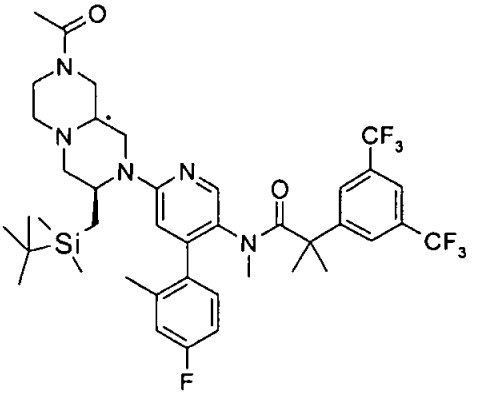
The starting (3*R*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol (D89, 528 mg, 3.08 mmol) was dissolved in 20 mL of dichloromethane and treated with Et_3N (1.29 mL, 9.25 mmol) and TDBMSCl (929.5 mg, 6.17 mmol). The reaction was stirred at room temperature overnight and then for additional 24 h. It was checked by UPLC/MS, which showed conversion to product: peak at 0.47 min, m/z = 286 (M+1), 172 (M-TBDMS+1). The crude was purified by flash chromatography (silica, CH_2Cl_2 : (0.5 M NH_3 in MeOH) 98:2 to 85:15). The residue obtained evaporating the fractions containing the product was dissolved in dichloromethane:MeOH 90:10 and the insoluble material was filtered away. The solutin was evaporated to give 638 mg of the target product.
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.02 - 4.15 (m, 1 H) 3.82 - 3.95 (m, 1 H) 3.52 - 3.67 (m, 2 H) 3.30 - 3.49 (m, 3 H) 3.03 - 3.19 (m, 1 H) 2.91 - 3.03 (m, 1 H) 2.66 - 2.89 (m, 6 H) 1.50 (t, 1 H) 0.85 - 0.96 (m, 9 H) 0.05 - 0.16 (m, 6 H).

Description 91: (7*R*,9a*S or 9aR*)-2-acetyl-7-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D91 – Diastereisomer 2)



To a solution of (3*R*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D90, 635 mg, 2.224 mmol) in 15 mL of dichloromethane was added triethylamine (620 µL, 4.45 mmol) and it was brought to – 10 °C. A solution of acetyl chloride (79 µL, 1.11 mmol, 0.5 eq.) in 0.5 mL of dichloromethane was added dropwise. The reaction was brought to – 45 °C and additional 0.25 eq. (39.5 µL) of acetyl chloride diluted in 0.5 mL of dichloromethane were added. The temperature was lowered to – 50 °C and 0.25 eq. (39.5 µL) of acetyl chloride diluted in 0.5 mL of dichloromethane were added again. The crude was purified by flash chromatography (silica, CH_2Cl_2 to CH_2Cl_2 : (0.5 M NH_3 in MeOH) 95:5). A sample of clean title compound was thus obtained: 121 mg.
MS (direct): m/z=328 (M+1)
1H NMR (500 MHz, DMSO-d_6) δ ppm 4.25 (d, 1 H) 3.77 (t, 1 H) 3.67 - 3.74 (m, 2 H) 3.11 (t, 1 H) 2.63 - 2.78 (m, 2 H) 2.53 - 2.61 (m, 2 H) 2.34 - 2.46 (m, 2 H) 2.11 (dd, 1 H) 1.95 - 2.03 (m, 1 H) 1.96 (s, 3 H) 1.82 - 1.90 (m, 1 H) 0.83 - 0.90 (m, 9 H) 0.04 (s, 6 H).

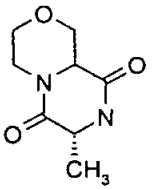
Description 92: *N*-[6-((3*R*,9a*S or 9aR*)-8-acetyl-3-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D92 - Diastereoisomer 2)



To a solution of (7*R*,9a*S or 9aR*)-2-acetyl-7-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D91,

117 mg, 0.357 mmol) in 1.5 mL of toluene was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (146.5 mg, 0.275 mmol), bis-tri –tert-butylphosphine palladium (28 mg, 0.055 mmol), hexadecyltrimetylammonium chloride (18 μL of a 25% aqueous solution) and, at last, sodium hydroxide solution (33 μL of a 50% aqueous solution). The solution was degassed by freeze-pump-thaw cycles, then stirred at 90°C for 3 h. It was checked by UPLC/MS, which showed peaks for the expected product at 1.21 min. (m/z = 824 (M+1), 412 (M+2)/2). The solution was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine. The title compound was isolated by flash chromatography (silica, cyclohexane:EtOAc 50:50 -> 0:100), obtaining 199 mg that were brought directly to the next step.

Description 93: (3*R*)-3-methyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D93)

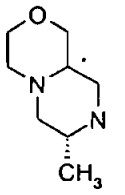


To a solution of *N*-boc-morpholine-3-carboxylic acid (2 g, 9.379 mmol) in 60 mL of dichloromethane and was added TBTU (3.313 g, 10.32 mmol) and diisopropylethyl amine (1.96 mL, 11.25 mmol). The reaction was stirred for 30 min. In the meantime, a solution of D-alanine methyl ester hydrochloride (1.93 g, 18.76 mmol) and diisopropylethylamine (3.27 mL, 18.76 mmol) in 20 mL of dichloromethane was prepared and finally added to the reaction mixture. The reaction was left stirring at room temperature for 2 h. UPLC-MS analysis showed the expected product (peak at 0.60 min, m/z = 317 (M+1), 261 (M - *t*-Bu+1), 217 (M – Boc +1)). The reaction was diluted with dichloromethane and extracted with sat. $NaHCO_3$, dried (Na_2SO_4), and the solvent removed. The crude (5.56 g) was taken to the next step without further purification.

It was dissolved in 50 mL of dichloromethane and treated with 50 mL of TFA, added at 0°C. The reaction was stirred at room temperature for 30 min. It was checked by UPLC/MS, which showed the expected deprotection product. The crude was purified by SCX. The fractions containing the product were concentrated and the resulting solution was stirred at 50°C for 9 h and at 80°C for additional 19 h. UPLC/MS analysis showed formation of the cyclized product: peak at 0.34 min, m/z= 185 (M+1). The solution was run through a SCX cartridge and thus was obtained the title compound, 1.095 g.

1H NMR (400 MHz, DMSO-d_6) δ ppm 8.36 (br. s., 1 H) 3.80 - 4.22 (m, 5 H) 3.33 - 3.41 (m, 2 H) 2.68 - 2.84 (m, 1 H) 1.25 - 1.37 (m, 3 H).

Description 94 and 95: (7*R*,9a*R or 9aS*)-7-methyloctahydropyrazino[2,1-*c*][1,4]oxazine (D94- Diastereoisomer 1) and (7*R*,9a*S or 9aR*)-7-methyloctahydropyrazino[2,1-*c*][1,4]oxazine (D95- Diastereoisomer 2)

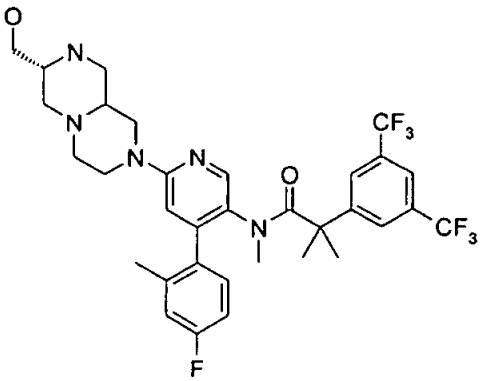


To a flask containing (3*R*)-3-methyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione, mix of diastereomers, (D93, 923 mg, 5.01 mmol) was added 1M BH_3-THF solution (50 mL) and it was heated to 90°C for 14 h. To the suspension were added 30 mL of 6M HCl and it was heated to 90°C for 2 h. MS analysis: m/z= 157 (M+1 of the target product). The reaction mixture was purified by SCX, followed by flash chromatography (silica, dichloromethane: (NH_3 in MeOH) = 95:5 to 80:20. The two title compounds were isolated:

Diastereoisomer 1 (D94) (102 mg):
1H NMR (400 MHz, DMSO-d_6) δ ppm 3.65 - 3.73 (m, 1 H) 3.53 - 3.60 (m, 1 H) 3.43 - 3.52 (m, 1 H) 3.02 (t, 1 H) 2.68 - 2.81 (m, 1 H) 2.52 - 2.68 (m, 3 H) 2.25 (t, 1 H) 2.07 - 2.19 (m, 1 H) 1.88 - 2.00 (m, 1 H) 1.68 (t, 1 H) 0.91 (d, 3 H)

Diastereoisomer 2 (D95) (29 mg):
1H NMR (400 MHz, DMSO-d_6) δ ppm 3.63 - 3.72 (m, 1 H) 3.46 - 3.56 (m, 2 H) 3.09 (t, 1 H) 2.95 - 3.03 (m, 1 H) 2.31 - 2.47 (m, 3 H) 2.17 - 2.24 (m, 1 H) 2.06 - 2.17 (m, 1 H) 1.87 - 2.04 (m, 1 H) 1.21 - 1.28 (m, 1 H) 1.17 (d, 3 H)

Description 96: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*)-7-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (D96)



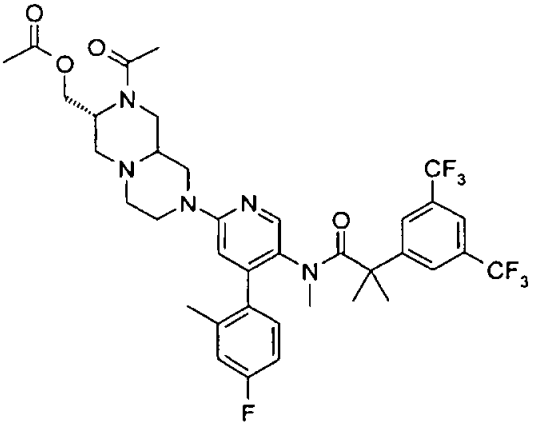
To a solution of (3*R*)-octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-ylmethanol (D89, Mixture of diastereoisomers of unknown ratio, 83.5 mg, 0.496 mmol) in 1.6 mL of

DMSO were added K_2CO_3 (78 mg) and 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (100 mg). The reaction was left at 150°C for 23 h. It was checked by UPLC/MS, which showed a peak for the expected product at 0.71 min. (m/z = 668 (M+1), 334 (M+2)/2). The solution was diluted with dichloromethane, extracted with water and dried (Na_2SO_4). The title ccompound obtained (113.5 mg) was taken to the next step without further purification.

1H NMR (400 MHz, DMSO-d_6) δ ppm 8.02 (br. s., 1 H) 7.88 (br. s., 1 H) 7.71 (br. s., 2 H) 7.01 - 7.25 (m, 3 H) 6.62 - 6.75 (m, 1 H) 4.38 - 4.58 (m, 1 H) 4.14 - 4.30 (m, 1 H) 4.00 - 4.15 (m, 1 H) 3.58 - 3.70 (m, 1 H) 3.49 - 3.59 (m, 1 H) 3.20 - 3.36 (m, 2 H) 2.79 - 2.93 (m, 2 H) 2.63 - 2.79 (m, 4 H) 2.02 - 2.35 (m, 6 H) 1.83 - 2.02 (m, 1 H) 1.13 - 1.58 (m, 6 H)

Ratio of Diastereoisomers not determined.

Description 97: {(3*R*)-2-acetyl-8-[5-[{2-[3,5-bis(trifluoromethyl)phenyl]-2-methylpropanoyl}(methyl)amino]-4-(4-fluoro-2-methylphenyl)-2-pyridinyl]octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-yl}methyl acetate (D97)



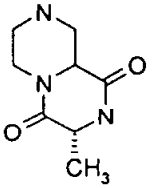
To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*)-7-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (D96, 56 mg, 0.0838 mmol) in 10 mL of dichloromethane were added Et_3N (35 μL) and a solution of acetyl chloride (15 μL) in dichloromethane (0.3 mL). The reaction was stirred at room temperature for 3 h. It was checked by UPLC/MS, which showed a peak for the expected product at 0.89 min. (m/z = 752 (M+1), 376 (M+2)/2). The solution was diluted with dichloromethane, extracted with water and dried (Na_2SO_4). The crude was purified by flash chromatography (cyclohexane to EtOAc), obtaining 28.5 mg of the title compound.

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.00 (br. s., 1 H) 7.78 (br. s., 1 H) 7.65 (br. s., 2 H) 6.80 - 7.08 (m, 3 H) 6.41 - 6.52 (m, 1 H) 4.42 - 4.70 (m, 2 H) 4.17 - 4.40 (m, 2 H) 3.95 - 4.17 (m, 2 H) 3.53 - 3.65 (m, 1 H) 2.98 - 3.26 (m, 2 H) 2.74 - 2.93 (m, 3 H) 2.49 - 2.74 (m, 3 H) 2.21 - 2.47 (m, 5 H) 2.02 - 2.21 (m, 9 H) 1.46 - 1.55 (m, 3 H)

100

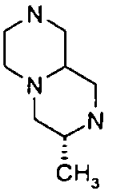
UPLC/MS: peak @ 0.89 min. m/z = 752 (M+1), 376 (M+2)/2.
Ratio of Diastereoisomers not determined.

Description 98: (3*R*)-3-methyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione (D98)



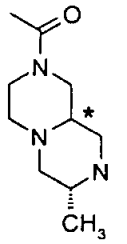
To a solution of *N,N'*-diboc-piperazine-2-carboxylic acid (2 g, 6.06 mmol) in 50 mL of dichloromethane and was added TBTU (2.138 g, 6.66 mmol) and diisopropylethyl amine (1.3 mL, 7.26 mmol). The reaction was stirred for 45 min. In the meantime, a suspension of D-alanine methyl ester hydrochloride (1.249 g, 12.11 mmol) and diisopropylethylamine (3.27 mL, 18.76 mmol) in 20 mL of dichloromethane and 5 mL of DMF was stirred and finally added to the reaction mixture. The reaction was left stirring at room temperature overnight. UPLC-MS analysis showed the expected product (peak at 0.72 min, m/z = 416 (M+1), 360 (M - *t*-Bu+1). The reaction was diluted with dichloromethane and extracted with sat. $NaHCO_3$, dried (Na_2SO_4), and the solvent removed. The crude (4.242 g) was taken to the next step without further purification.
It was dissolved in 50 mL of dichloromethane and to the solution was added dropwise TFA (50 mL) at 0°C. The reaction was stirred at room temperature for 2 h. It was checked by UPLC/MS. The reaction mixture was evaporated and the crude was purified by SCX. The fractions containing the product were collected and their volume reduced and the resulting solution was stirred at 60°C overnight. UPLC/MS analysis showed formation of the cyclized product: peak at 0.17 min, m/z= 184 (M+1). The solvent was removed and the residue taken treated in methanol. The white precipitate was collected by filtration, giving 353 mg of the title compound (additional 156 mg of precipitate formed from the solution).
1H NMR (400 MHz, DMSO-d_6) δ ppm 8.24 (br. s., 0.5 H) 7.96 (br. s., 0.5H) 3.79 - 4.29 (m, 2 H) 3.10 - 3.31 (m, 1 H) 2.73 - 3.11 (m, 2 H) 2.52 - 2.73 (m, 2 H) 1.30 (d, 1.5 H) 1.21 (d, 1.5 H)

Description 99: (3*R*)-3-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D99).



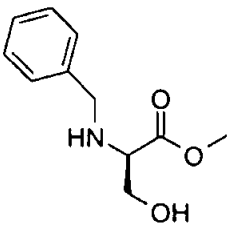
To a flask containing(3*R*)-3-methyltetrahydro-2*H*-pyrazino[1,2-*a*]pyrazine-1,4(3*H*,6*H*)-dione(D98, 353 mg, 1.927 mmol) was added 1M BH_3-THF solution (20 mL) and it was heated to reflux for 20 h. MS analysis: m/z= 156 (M+1 of the target product).To the reaction were added at 0°C 10 mL of 6M HCl and it was heated to 90°C for 20 h. The reaction mixture was purified by SCX, obtaining 243 mg of the target compound.
1H NMR (400 MHz, DMSO-d_6) consistent with a mixture of diastereomers of the target compound.

Description 100 and 101: (7*R*,9a*R or 9aS*)-2-acetyl-7-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D100, Diastereoisomer 1) and (7*R*,9a*S or 9aR*)-2-acetyl-7-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D101, Diastereoisomer 2)



To a solution (3*R*)-3-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D99, 243 mg, 1.232 mmol) in DMF (35 mL) was added triethylamine (260 µL, 1.848 mmol). The solution was cooled to -60°C and a solution of acetic anhydride (95 µL, 0.986 mmol) in DMF (3mL) was added dropwise. The reaction was allowed to reach -60°C slowly. UPLC/MS analysis: peaks @ 0.18 and 0.24 min, both m/z= 198 (M+1 of the target product). The reaction mixture was purified by SCX, followed by flash chromatography (silica, dichloromethane to dichloromethane:MeOH 85:15) Two different samples were thus obtained:
Diastereoisomer 1 (D100) (101.5 mg):
1H NMR (500 MHz, DMSO-d_6) δ ppm 4.26 (dd, 1 H) 4.16 (dd, 1 H) 2.52 - 2.82 (m, 5 H) 2.26 - 2.33 (m, 1 H) 2.16 (t, 1 H) 1.96 (s, 3 H) 1.83 - 1.90 (m, 1 H) 1.56 - 1.70 (m, 2 H) 0.90 (d, 3 H)
Diastereoisomer 1 and 2 (D100 plus D101) (75 mg):
The NMR sample consisted of a mixture of two components, ratio ca. 3:1. The major component is equal to Diastereoisomer 1. The minor one appears consistent with its Diastereoisomer 2.

Description 102: Methyl *N*-(phenylmethyl)-D-serinate (D102)

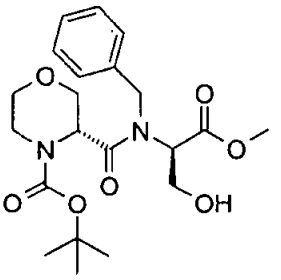


The title compound was prepared according to literature (ref. *JOC*, **1990**, *55*(1), 111-122) starting from (D)-serine methyl ester hydrochloride (98%, from Aldrich)

(D)-serine methyl ester hydrochloride (10g, 0.065 moles) was suspended in 50 ml of anhydrous methanol and cooled to 0°C under nitrogen. Triethylamine (9 ml, 0.065 moles) was added dropwise, followed by benzaldehyde (6.6 ml, 0.065 moles). The reaction mixture was then warmed up and stirred at room temperature for 2 hours. Sodium borohydride (4.85g, 0.13 moles) were added in small portions over 2 hours. The resulting mixture was stirred at room temperature overnight. The mixture was then slowly added to 50 ml of HCl (20% solution) at 0°C and the resulting solution was washed with diethyl ether (50 ml). The aqueous layer was then brought to basic pH by adding solid potassium carbonate and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as colourless oil (10.95g).

m/z = 210 $[M+H]^+$

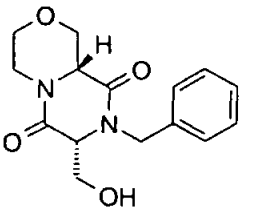
Description 103: 1,1-dimethylethyl (3*R*)-3-{[[(1*R*)-1-(hydroxymethyl)-2-(methyloxy)-2-oxoethyl](phenylmethyl)amino]carbonyl}-4-morpholinecarboxylate (non-preferred name) (D103)



To a stirred suspension of (R)-4-Boc-morpholine-3-carboxylic acid (30g, 0.13 moles, from J&W PharmLab) in 500 ml of anhydrous DCM at room temperature under nitrogen, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (37.4g, 0.195 moles) and 1-hydroxybenzotriazole hydrate (19.3g, 0.143 moles) were added in portions. At the end of addition the suspension became almost a clear solution. The mixture was stirred at room temperature for 45 minutes and then Methyl *N*-(phenylmethyl)-D-serinate (D102, 28.6g, 0.137 moles) and N,N-diisopropylethylamine (45.3 ml, 0.26 moles) were added in small portions. The

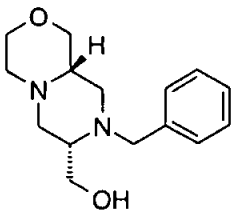
mixture was stirred at room temperature for 26 hours and then was additioned with ammonium chloride (sat. solution, 250 ml) and DCM (150 ml). Phases were separated and the aqueous layer was extracted with DCM (3 x 150 ml) and EtAc (1 x 200ml). The combined organic extracts were washed with brine (2 x 500 ml), dried (Na_2SO_4), concentrated under vacuum and the residue purified by silica gel chromatography eluting with 0 to 30% EtOAc/Cyclohexane to afford the title compound as yellow oil (38.7g).
UPLC/MS: peak at Rt = 0.62 min with m/z = 423.1 $[M+H]^+$

Description 104: (7*R*,9a*R*)-7-(hydroxymethyl)-8-(phenylmethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione) (D104)



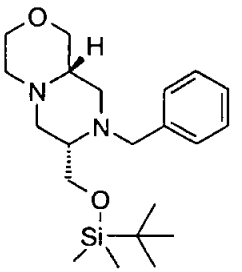
To a stirred solution of 1,1-dimethylethyl (3*R*)-3-{[[(1*R*)-1-(hydroxymethyl)-2-(methyloxy)-2-oxoethyl](phenylmethyl)amino]carbonyl}-4-morpholinecarboxylate (D103, 38.7g, 0.092 moles) in 400 ml of DCM at room temperature, trifluoroacetic acid (68.3 ml, 0.92 moles) was slowly added. The resulting orange solution was stirred at room temperature overnight. It was then cooled by an ice-water bath and brought to pH = 7-8 by adding sodium hydrogen carbonate (sat. solution, 250 ml and as solid). Phases were separated and the aqueous layer was extracted with DCM (3 x 300 ml). The combined organic extracts were dried (Na_2SO_4), concentrated under vacuum to afford a residue, which was dissolved in 270 ml of methanol and heated to 56-58°C for 2 hours. The mixture was then allowed to cool down to room temperature and the solvent was removed under vacuum to afford a solid residue, which was treated with 100 ml of a mixture cyclohexane/EtOAc 8/2. The resulting suspension was stirred at room temperature for 30-40 minutes and then the solid was filtered off and collected to afford the title compound (18.7g) as white solid.
UPLC/MS: peak at Rt = 0.49 min with m/z = 291.09 $[M+H]^+$
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.26 - 7.37 (m, 5 H) 5.41 (t, 1 H) 5.09 (d, 1 H) 4.31 (dd, 1 H) 4.23 (dd, 1 H) 4.01 - 4.07 (m, 2 H) 3.69 - 3.84 (m, 4 H) 3.59 (t, 1 H) 3.33 (td, 1 H) 2.85 (td, 1 H).

Description 105: [(7*S*,9a*S*)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazin-7-yl]methanol (D105)



To a stirred suspension of (7*R*,9a*R*)-7-(hydroxymethyl)-8-(phenylmethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione) (D104, 18.7g, 0.064 moles) in 190 ml of anhydrous THF at 0°C under nitrogen, borane (THF complex solution, 1M in THF, 385 ml, 0.386 moles) was added over 45 minutes keeping the internal temperature below 10°C. At the end of the addition the mixture became a colourless solution. The mixture was then allowed to warm to room temperature and then heated to 70°C for 28 hours.
The mixture was then allowed to cool down to room temperature and then to 0°C by an ice-water bath. Methanol (47 ml, 1.15 moles) and HCl 6M (32 ml, 0.128 moles) were then slowly added, carefully monitoring the gas evolution. The resulting mixture was then allowed to warm to room temperature and stirred overnight. The mixture was then heated to 55°C for 8 hours and then cooled down to room temperature. The white precipitate was filtered off and the filtrate was concentrated under vacuum to afford a residue, which was dissolved in 50 ml of water and 100 ml of DCM. The white precipitate which was previously filtered off was collected and dissolved in 70 ml of water and added to the previous mixture. Phases were separated and the aqueous layer was extracted with DCM (3 x 150 ml). The aqueous layer was then brought to pH = 7 by adding 250 ml of NaOH 3N and extracted again with DCM (3 x 100 ml) and ethyl acetate (3 x 200 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as pale yellow foam (16.9g).
UPLC/MS: peak at Rt = 0.40 min with m/z = 263.13 $[M+H]^+$

Description 106 : (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D106)



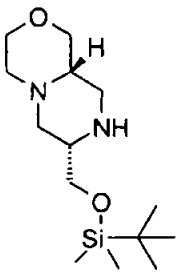
Method a) :
To a stirred solution of [(7*S*,9a*S*)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazin-7-yl]methanol (D105, 15.3g, 0.058 moles) in 153 ml of DCM at room

temperature, imidazole (4.76g, 0.070 moles) and *tert*-butyldimethylsilyl chloride (8.35g, 0.055 moles) were added. The resulting mixture was stirred at room temperature for 1 hour. Imidazole (0.476g, 5.8 mmoles) and *tert*-butyldimethylsilyl chloride (8.35g, 0.055 moles) were then added a second time and the mixture stirred overnight. Imidazole (0.476g, 0.006 moles) and *tert*-butyldimethylsilyl chloride (5.27g, 0.035 moles) were then added a third time and the mixture stirred for further 4 hours. DCM (153 ml) was added and the imidazole (2.4, 0.035 moles) and *tert*-butyldimethylsilyl chloride (5.27g, 0.035 moles) were then added a fourth time. The mixture was stirred overnight. Water (150 ml) and sodium hydrogen carbonate (sat. solution, 150 ml) were then added and phases were separated. The aqueous layer was extracted with DCM (150 ml) and the combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to a residue, purified by silica gel chromatography eluting with 5 to 10% EtOAc/Cyclohexane to afford the title compound as an oil (22.2g).

1H NMR (500 MHz, DMSO-d_6) δ ppm 7.32 - 7.36 (m, 4 H) 7.24 - 7.29 (m, 1 H) 4.00 (t, 1 H) 3.90 (dd, 1 H) 3.88 (d, 1 H) 3.77 (dd, 1 H) 3.70 (d, 1 H) 3.52 - 3.58 (m, 1 H) 3.48 - 3.56 (m, 1 H) 3.07 (t, 1 H) 2.75 - 2.83 (m, 2 H) 2.25 - 2.37 (m, 4 H) 2.12 - 2.23 (m, 2 H) 0.90 (s, 9 H) 0.08 (s, 3 H) 0.06 (s, 3 H)
HPLC (walk-up): Rt = 4.826 min (area % = 98.69)

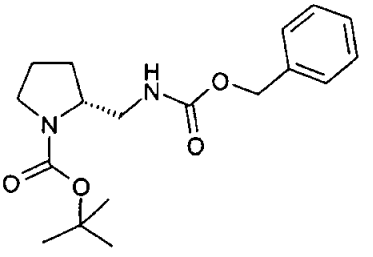
Method b) :
To a stirred solution of [(7*S*,9a*S*)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazin-7-yl]methanol (D105, 29.8g, 0.114 moles) in 447 ml of DCM at room temperature, imidazole (9.27g, 0.136 moles) and *tert*-butyldimethylsilyl chloride (42.7g, 0.284 moles) were added. The resulting mixture was stirred at room temperature overnight. Water (300 ml), sodium hydrogen carbonate (sat. solution, 300 ml) and DCM (150 ml) were then added and phases were separated. The aqueous layer was extracted with DCM (300 ml) and the combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to a residue, purified by silica gel chromatography eluting with 5 to 10% EtOAc/Cyclohexane to afford the title compound as light yellow oil (50.95g).
HPLC (walk-up): Rt = 4.865 min (area % = 99.55).

Description 107: (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1*c*][1,4]oxazine (D107)



To a stirred solution of (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D106, 22.2g, 0.059 moles) in 660 ml of methanol at room temperature under nitrogen, palladium on carbon (10 wt%, wet, 6.28g, 0.006 moles) and ammonium formate (37.2g, 0.59 moles) were added. The resulting mixture was stirred at 80°C for 1-1.5 hours. The resulting mixture was then allowed to cool down to room temperature and filtered over Celite. The filtrate was concentrated under vacuum to afford the title compound (16 g) as pale yellow oil.
UPLC/MS: no UV visible peak. Mass m/z = 287.18 $[M+H]^+$
CASS ID 8341, NMR and LC/MS
1H NMR (500 MHz, DMSO-d_6) δ ppm 3.74 (t, 1 H) 3.62 - 3.70 (m, 2 H) 3.48 (dd, 1 H) 3.39 - 3.46 (m, 1 H) 2.98 (t, 1 H) 2.67 - 2.73 (m, 1 H) 2.60 (dd, 1 H) 2.40 (dd, 1 H) 2.26 - 2.37 (m, 2 H) 2.23 (br. s., 1 H) 2.12 (dd, 1 H) 2.04 - 2.10 (m, 1 H) 1.90 - 2.00 (m, 1 H) 0.81 (s, 9 H) -0.00 (s, 6 H)
ROESY cross peak pattern in accordance with the syn relative stereochemistry.

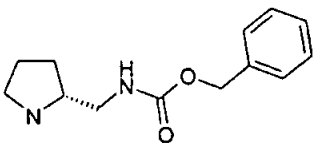
Description 108: 1,1-dimethylethyl (2*R*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinecarboxylate)(D108)



To a solution of (R)-2-(Aminomethyl)-1-N-Boc-pyrrolidine (1.6 g, 8 mmol) in 25 mL of dichloromethane was added DIPEA (2.09 mL, 12 mmol) and at 0°C Benzyl Chloroformate (1.36 mL, 9.6 mmol). The reaction mixture was warmed-up to r.t. and then it was stirred for 3 hrs at this temperature.
Brine was added to the reaction mixture, the aqueous phase was extracted with dichloromethane and the combined organic phases were dried and evaporated to dryness. The crude was purified by chromatography (silica cartridge, cyclohexane:EtOAc 9:1) to give the title compound (2.07 g, y=77%).

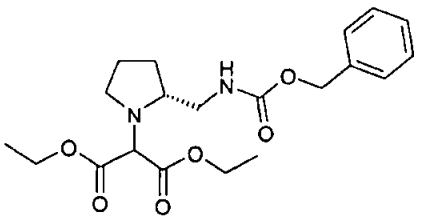
MS: m/z= 357 (M+Na) and 235 (M-BOC+1).
1H NMR (400 MHz, DMSO-d_6) δ ppm 6.98 - 7.49 (m, 6 H) 4.88 - 5.15 (m, 2 H) 3.58 - 3.83 (m, 1 H) 3.05 - 3.32 (m, 3 H) 2.75 - 3.04 (m, 1 H) 1.52 - 1.98 (m, 4 H) 1.20 - 1.49 (m, 9 H)

Description 109:
phenylmethyl [(2*R*)-2-pyrrolidinylmethyl]carbamate (D109)



To a solution of 1,1-dimethylethyl (2*R*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinecarboxylate (D108, 2.07 g, 6.1 mmol) in 16 ml of dichloromethane, cooled to 0°C, were added 4 ml of TFA. The reaction mixture was allowed to warm-up to r.t. and then it was stirred at this temperature for 30 mins. The title compound (1.06 g, y=88%) was isolated after purification by SCX.
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.00 - 7.66 (m, 5 H) 4.90 - 5.20 (m, 2 H) 3.12 - 3.24 (m, 1 H) 2.97 - 3.09 (m, 1 H) 2.84 - 2.97 (m, 2 H) 2.61 - 2.82 (m, 2 H) 1.44 - 1.83 (m, 3 H) 1.14 - 1.40 (m, 1 H)

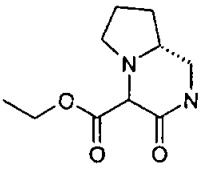
Description 110: diethyl {(2*R*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinyl}propanedioate (D110)



To a mixture of phenylmethyl [(2*R*)-2-pyrrolidinylmethyl]carbamate (D109, 1.26 g, 5.38 mmol) and K_2CO_3 (1.48 g, 10.76 mmol) in acetonitrile (20 ml), cooled to 0°C, was added dropwise diethyl bromomalonate (1.08 ml, 6.46 mmol) in a 2-3 mins time. Then the reaction mixture was allowed to warm-up to r.t. and it was stirred at this temperature for 2.5 hrs. Further diethyl bromomalonate (1.08 ml, 1.6 mmol) was added and the reaction mixture was stirred for one more hour.
The solvent was removed, water was added and it was extracted with EtOAc. The crude was purified by chromatography (silica cartridge, cyclohexane:EtOAc 95:5) to give the title compound (1.07 g).

MS: m/z= 393 (M+1) and 415 (M+Na)
UPLC/MS: m/z= 393 (M+1) @ t=0.79 min
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 - 7.45 (m, 5 H) 7.08 - 7.23 (m, 1 H) 4.91 - 5.06 (m, 2 H) 4.40- 4.50 (m, 1 H) 3.93 - 4.23 (m, 4 H) 2.94 - 3.14 (m, 3 H) 2.70 - 2.90 (m, 2 H) 1.45 - 1.89 (m, 4 H) 1.07 - 1.28 (m, 6 H)

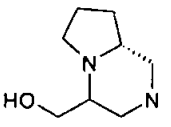
Description 111: ethyl (8a*R*)-3-oxooctahydropyrrolo[1,2-*a*]pyrazine-4-carboxylate (D111)



The solution of diethyl {(2*R*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinyl}propanedioate (D110, 1.07 g, 2.72 mmol) in EtOH (ca. 20 ml) was degassed, (10%) Pd/C (580 mg) was added and the reaction mixture was stirred under a H_2 atmosphere for 2.5 hrs. The catalyst was filtered off and the volume of the filtrated solution was reduced in vacuo. The solution was warmed-up to 50°C and it was stirred at this temperature for 6 hrs and at room temperature for 12 hrs. The solvent was evaporated to dryness to give the title compound (617 mg) as a mixture of diastereoisomers (ratio ca. 70:30). This crude was used in the next step without further purification.
MS: m/z= 213 (M+1)
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.93 - 8.12 (m, 1 H) 4.03 - 4.27 (m, 3 H) 3.15 - 3.30 (m, 1 H) 2.91 - 3.07 (m, 1 H) 2.77 - 2.93 (m, 1 H) 2.37 - 2.47 (m, 1 H) 2.03 - 2.15 (m, 1 H) 1.63 - 1.94 (m, 3 H) 1.26 - 1.50 (m, 1 H) 1.04 - 1.28 (m, 3 H)

The ratio between the two diastereoisomers was determined on the basis of the integral ratio of diagnostic peaks such as the N-H lactam signals found in 7.93 - 8.12 range.

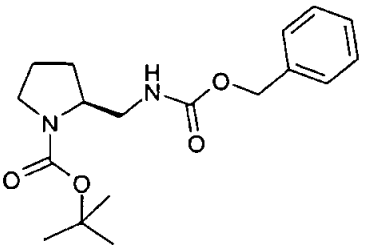
Description 112: (8a*R*)-octahydropyrrolo[1,2-*a*]pyrazin-4-ylmethanol (D112)



To a solution of ethyl (8a*R*)-3-oxooctahydropyrrolo[1,2-*a*]pyrazine-4-carboxylate (D111, 207 mg, 0.976 mmol) in THF (0.5 ml) was added 2M $LiBH_4$ in THF (1.46 ml) and the reaction mixture was refluxed for 17 hrs. The reaction mixture was cooled

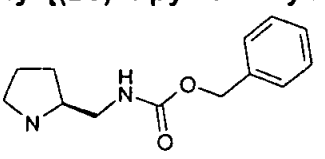
down to r.t., 9.7 ml of 1M BH_3-THF were added and the mixture was refluxed for 2 hrs.
The reaction mixture was cooled down to 0°C and 4 ml of MeOH were added. Then 1.5 ml of conc. HCl were added at 0°C and the reaction mixture was refluxed for 1 hr. The solvent was evaporated to dryness and the crude was purified by SCX cartridge and then by chromatography (silica, CH_2Cl_2: 2M NH_3 in MeOH 9:1 to 8:2) to give the title compound (73 mg) as a mixture of diastereoisomers.
MS: m/z= 157 (M+1)
1H NMR (300 MHz, DMSO-d_6) δ ppm 4.2 - 4.4 (m, 1 H) 3.44 - 3.63 (m, 1 H) 3.04 - 3.22 (m, 2 H) 2.54 - 2.97 (m, 4 H) 2.05 - 2.31 (m, 1 H) 1.84 - 2.03 (m, 1 H) 1.40 - 1.85 (m, 3 H) 0.99 - 1.32 (m, 1 H)

Description 113: 1,1-dimethylethyl (2*S*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinecarboxylate (D113)



To a solution of (S)-2-(Aminomethyl)-1-N-Boc-pyrrolidine (1.65 g, 8.25 mmol) in 25 mL of dichloromethane was added DIPEA (2.15 mL, 12.3 mmol) and at 0°C Benzyl Chloroformate (1.41 mL, 9.9 mmol). The reaction mixture was warmed-up to r.t. and then it was stirred for 3 hrs at this temperature.
Brine was added to the reaction mixture, the aqueous layer was extracted with dichloromethane and the combined organic phases were dried and evaporated to dryness. The crude was purified by chromatography (silica cartridge, cyclohexane:EtOAc 9:1) to give the title compound (2.23 g, y=80%).
MS: m/z= 235 (M-BOC+1)
UPLC/MS: m/z= 235 (M-BOC+1); 335 (M+1) @ t=0.8 min
1H NMR (400 MHz, DMSO-d_6) δ ppm 6.98 - 7.49 (m, 6 H) 4.88 - 5.15 (m, 2 H) 3.58 - 3.83 (m, 1 H) 3.05 - 3.32 (m, 3 H) 2.75 - 3.04 (m, 1 H) 1.52 - 1.98 (m, 4 H) 1.20 - 1.49 (m, 9 H)

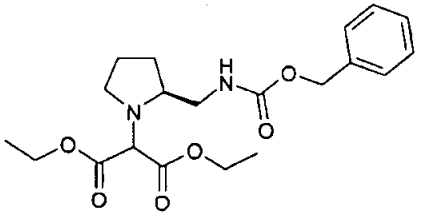
Description 114: phenylmethyl [(2*S*)-2-pyrrolidinylmethyl]carbamate (D114)



180

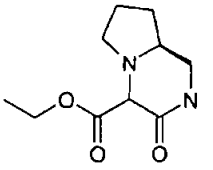
To a solution of 1,1-dimethylethyl (2*S*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinecarboxylate (D113, 2.23 g, 6.67 mmol) in 16 mL of dichloromethane, cooled to 0°C, were added 4 mL of TFA. The reaction mixture was allowed to warm-up to r.t. and then it was stirred at this temperature for 30 mins. The title compound was isolated as a colourless oil after purification by SCX (1.36 g).
MS: m/z= 235 (M-BOC+1)
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.04 - 7.47 (m, 6 H) 4.82 - 5.16 (m, 2 H) 3.11 - 3.46 (m, 1 H) 2.97 - 3.09 (m, 1 H) 2.84 - 2.97 (m, 2 H) 2.61 - 2.82 (m, 2 H) 1.40 - 1.83 (m, 3 H) 1.10 - 1.37 (m, 1 H)

Description 115: diethyl {(2*S*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinyl}propanedioate (D115)



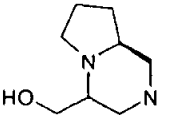
To a mixture of phenylmethyl [(2*S*)-2-pyrrolidinylmethyl]carbamate (D114, 1.36 g, 5.81 mmol) and K_2CO_3 (1.6 g, 11.62 mmol) in acetonitrile (20 ml), cooled to 0°C, was added dropwise diethyl bromomalonate (1.37 ml, 6.97 mmol) in a 2-3 mins time. Then the reaction mixture was allowed to warm-up to room temperature and it was stirred for 4 hrs.
The volume of the solvent was reduced, brine was added and it was extracted with dichloromethane. The combined organic phases were dried and evaporated to dryness. The crude was purified by chromatography (silica cartridge, cyclohexane:EtOAc 95:5 to 7:3) to give the title compound as a colourless oil (1.40 g, y=61%).
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.23 - 7.48 (m, 5 H) 7.09 - 7.21 (m, 1 H) 4.87 - 5.08 (m, 2 H) 4.40- 4.50 (m, 1 H) 3.98 - 4.23 (m, 4 H) 2.93 - 3.16 (m, 3 H) 2.62 - 2.91 (m, 2 H) 1.43 - 1.92 (m, 4 H) 1.00 - 1.30 (m, 6 H)

Description 116: ethyl (8a*S*)-3-oxooctahydropyrrolo[1,2-*a*]pyrazine-4-carboxylate (D116)



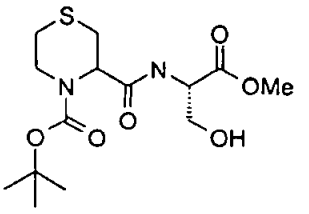
The solution of diethyl {(2*S*)-2-[({[(phenylmethyl)oxy]carbonyl}amino)methyl]-1-pyrrolidinyl}propanedioate (D115, 1.40 g, 3.67 mmol) in EtOH (ca. 20 ml) was degassed, (10%) Pd/C (778 mg, 0.734 mmol) was added and the reaction mixture was stirred under a H_2 atmosphere for 2.5 hrs. The catalyst was filtered off and the volume of the filtrated solution was reduced in vacuo. The solution was warmed-up to 50°C and it was stirred at this temperature for 7 hrs. The solvent was evaporated to dryness to give the title compound as a yellowish oil (793 mg) as a mixture of diastereoisomers. This crude was used in the next step without further purification.
MS: m/z= 213 (M +1)
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.90 - 8.11 (m, 1 H) 4.02 - 4.43 (m, 3 H) 3.15 - 3.30 (m, 1 H) 2.79 - 3.07 (m, 2 H) 2.36 - 2.56 (m, 1 H) 2.0 - 2.2 (m, 1 H) 1.63 - 2.18 (m, 3 H) 1.26 - 1.51 (m, 1 H) 1.13 - 1.27 (m, 3 H)

Description 117: (8a*S*)-octahydropyrrolo[1,2-*a*]pyrazin-4-ylmethanol (D117)



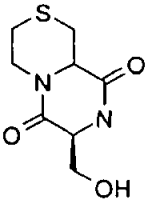
To a solution of ethyl (8a*S*)-3-oxooctahydropyrrolo[1,2-a]pyrazine-4-carboxylate (D116, 403 mg, 1.88 mmol) in THF (ca. 3 ml) was added 2M $LiBH_4$ in THF (1.41 ml, 2.83 mmol) and the reaction mixture was refluxed overnight. The reaction mixture was cooled down to r.t., 18.8 ml of 1M BH_3-THF were added and the mixture was refluxed for 2 hrs.
The reaction mixture was cooled down to 0°C and 8 ml of MeOH were added. Then 3 ml of conc. HCl were added and the reaction mixture was refluxed for ca. 2 hrs. The solvents were evaporated to dryness and the crude was purified by SCX to give the title compound as a colourless oil (220 mg). It's a mixture of diastereoisomers.
MS: m/z= 157 (M +1)
1H NMR (400 MHz, DMSO-d_6) δ ppm 4.29 - 4.47 (m, 1 H) 3.46 - 3.64 (m, 1 H) 3.10 - 3.45 (m, 2 H) 2.82 - 2.96 (m, 1 H) 2.50 - 2.81 (m, 3 H) 1.44 - 2.38 (m, 5 H) 1.01 - 1.31 (m, 1 H)

Description 118: 1,1-dimethylethyl 3-({[(1*S*)-1-(hydroxymethyl)-2-(methyloxy)-2-oxoethyl]amino}carbonyl)-4-thiomorpholinecarboxylate (D118)



To a solution of N-Boc thiomorpholine carboxylic acid (1.36 g, 5.51 mmol) in dichloromethane (13.6 ml) were added under N_2, at r.t., TBTU (1.95 g, 6.06 mmol) and DIPEA (1.92 ml, 11.02 mmol) and the solution was stirred for 30 mins. To a suspension of L-serine methyl ester hydrochloride (1.71 g, 11.02 mmol) in dichloromethane (13.6 ml) was added DIPEA (1.92 ml, 11.02 mmol) and the resulting solution was stirred for 30 mins. Then the solution containing the serine free base was added to the reaction mixture and it was left stirring for 16 hrs. Water was added to the reaction mixture and the aqueous layer was extracted with dichloromethane (x3) and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The crude title compound (3.87 g) was used in the next step without further purification.
UPLC/MS: m/z= 371 (M+Na); 349 (M+1); 293 (M-*t*Bu); 249 (M-BOC+1) @ t=0.59 min

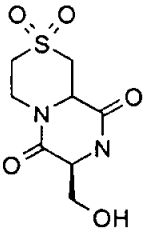
Description 119: (7*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione(D119)



To a solution of the crude 1,1-dimethylethyl 3-({[(1*S*)-1-(hydroxymethyl)-2-(methyloxy)-2-oxoethyl]amino}carbonyl)-4-thiomorpholinecarboxylate (D118, 3.87 g) in 44 ml of dichloromethane were added under N_2, at r.t., 22 ml of TFA. The reaction mixture was stirred at room temperature for 3 hrs. The solvents were removed under reduced pressure and the residue was purified on a SCX cartridge. The fraction eluted with 2M methanolic ammonia was evaporated to dryness and the residue was dissolved in MeOH and refluxed for 20 hrs.
The reaction mixture was evaporated to dryness and the desired product was purified by SCX, eluting with MeOH. The title compound (1.1 g, y=92% over 2 steps) was isolated as a mixture of diastereoisomers (ratio ~ 50/50).
UPLC/MS: 1st peak m/z= 217 (M+1) @ t=0.35 min; 2nd peak m/z= 217 (M+1) @ t=0.36 min

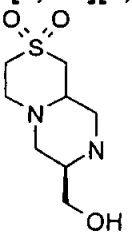
1H NMR (400 MHz, DMSO-d_6) δ ppm 8.07 - 8.31 (m, 1 H) 4.62 - 4.82 (m, 1 H) 3.95 - 4.18 (m, 1 H) 3.69 - 3.95 (m, 2 H) 3.30 - 3.66 (m, 2 H) 2.85 - 3.02 (m, 1 H) 2.69 - 2.86 (m, 2 H) 2.52 - 2.68 (m, 1 H).
The ratio between the two diastereoisomers was determined on the basis of the integral ratio of diagnostic peaks such as the N-H lactam signals found in 8.07 - 8.31 range.

Description 120:
(7*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione 2,2-dioxide (D120)



To a suspension of (7*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione (D119, 1.1 g, 5.09 mmol) in dichloromethane (22 ml) was added at r.t. 77% m-CPBA (2.85 g, 12.73 mmol) and the reaction mixture was stirred at room temperature for 2 hrs. The solvent was removed under reduced pressure and the crude was purified by chromatography (silica, CH_2Cl_2: 2M NH_3 in MeOH 98:2 to 8:2) to give the title compound as a white solid (900 mg, y=71%) as a mixture of diastereoisomers (ratio ~ 60/40).
MS: m/z= 249 (M+1) and 271 (M+Na)
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.29 - 8.54 (m, 1 H) 5.02 - 5.59 (m, 1 H) 4.59 - 4.89 (m, 1 H) 4.16 - 4.47 (m, 1 H) 3.86 - 3.99 (m, 1 H) 3.69 - 3.86 (m, 1 H) 3.50 - 3.68 (m, 1 H) 3.21 - 3.48 (m, 3 H) 2.91 - 3.20 (m, 2 H)
The ratio between the two diastereoisomers was determined on the basis of the integral ratio of diagnostic peaks such as the O-H alcohol signals found in 5.02 - 5.59 range.

Description 121:
[(7*R*)-2,2-dioxidooctahydropyrazino[2,1-*c*][1,4]thiazin-7-yl]methanol (D121)



To a suspension of (7*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]thiazine-6,9-dione 2,2-dioxide (D120, 900 mg, 3.63 mmol) in THF (10 ml) were added under N_2, at r.t., 36.3 ml of 1M BH_3-THF solution. The reaction mixture was refluxed for 16 hrs.

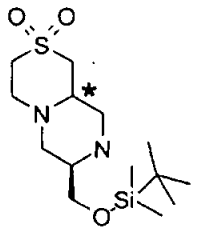
6 N HCl (20 ml) was added to the reaction mixture, cooled to 0°C, and the resulting mixture was refluxed for 2 hrs. Then the reaction mixture was evaporated to dryness and the crude was purified by SCX to give the title compound as a white foam (753 mg, y=94%)

MS: m/z= 221 (M+1) and 243 (M+Na)

1H NMR (300 MHz, DMSO-d_6) δ ppm 4.40 - 4.63 (m, 1 H) 3.33 - 3.48 (m, 1 H) 2.95 - 3.27 (m, 4 H) 2.72 - 2.95 (m, 3 H) 2.53 - 2.72 (m, 2 H) 2.20 - 2.41 (m, 2 H) 1.98 - 2.18 (m, 1 H) 1.65 - 1.85 (m, 1 H).

Description 122 and 123:

(7*R*,9a*R* or 9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]thiazine 2,2-dioxide(Description 122- Diastereoisomer 1) and (7*R*,9a*S* or 9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]thiazine 2,2-dioxide (Description 123- Diastereisomer 2)



To a suspension of [(7*R*)-2,2-dioxidooctahydropyrazino[2,1-*c*][1,4]thiazin-7-yl]methanol (D121, 753 mg, 3.42 mmol) in dichloromethane (30 ml) were added at r.t. Et_3N (1.9 ml, 13.68 mmol) and TDBMSCl (1.5 g, 10.3 mmol). The reaction mixture was stirred for 16 hrs at r.t..

Sat. $NaHCO_3$ was added and the aqueous phase was extracted with dichloromethane (x3) and the combined organic phases were dried and evaporated to dryness. The crude was purified by chromatography (silica, CH_2Cl_2:MeOH 1:0 to 97:3) to the title compounds:

D122- Diastereoisomer1 (566 mg, colourless oil):

MS: m/z= 335 (M+1)

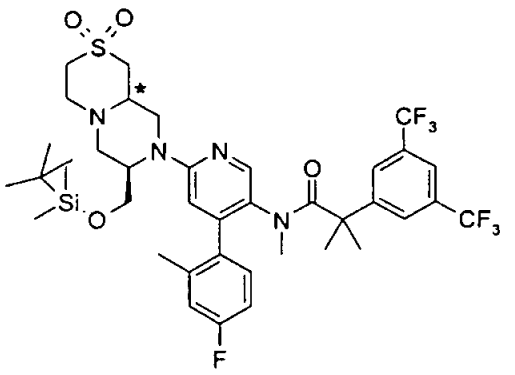
1H NMR (500 MHz, DMSO-d_6) δ ppm 3.47 - 3.66 (m, 2 H) 2.99 - 3.27 (m, 3 H) 2.80 - 2.95 (m, 3 H) 2.67 - 2.80 (m, 3 H) 2.56 - 2.66 (m, 2 H) 2.21 - 2.34 (m, 1 H) 0.55 - 1.11 (s, 9 H) -0.23 - 0.26 (s, 6 H)

D123- Diastereoisomer2 (382 mg, white solid):

MS: m/z= 335 (M+1)

1H NMR (500 MHz, DMSO-d_6) δ ppm 3.39 - 3.48 (m, 1 H) 3.31 - 3.40 (m, 1 H) 3.13 (t, 1 H) 2.91 - 3.09 (m, 3 H) 2.70 - 2.85 (m, 3 H) 2.56 - 2.65 (m, 1 H) 2.42 - 2.51 (m, 1 H) 2.19 - 2.36 (m, 2 H) 1.91 - 2.06 (m, 1 H) 1.74 (t, 1 H) 0.80 (s, 9 H) -0.02 (s, 6 H)

Description 124: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*R*,9a*R or 9aS*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D124- Diastereoisomer 1)



To a solution of (7*R*,9a*R* or 9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]thiazine 2,2-dioxide (D122, 120 mg, 0.36 mmol) in 2.2 ml of toluene were added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (147 mg, 0.28 mmol), bis-tri–tert-butylphosphine palladium (29 mg), hexadecyltrimetylammonium chloride (17.8 µL of a 25% aqueous solution) and sodium hydroxide solution (36 µL of a 50% aqueous solution). The reaction mixture was degassed by freeze-pump-thaw cycles and then it was stirred at 90°C for 4 hrs.

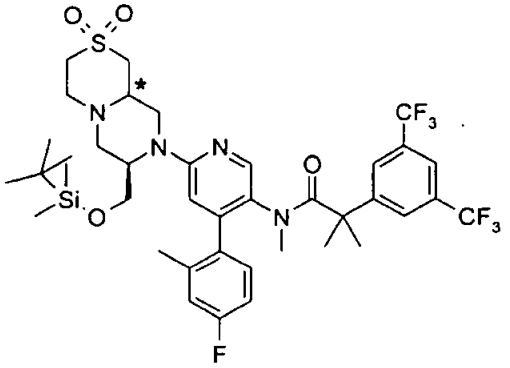
EtOAc and sat. $NaHCO_3$ aq. were added to the reaction mixture and the aqueous phase was extracted with EtOAc (x3). The combined organic phases were dried and evaporated to dryness. The crude was purified by chromatography (silica, cyclohexane:EtOAc 7:3 to 0:1) to give the title compound as a white solid (201 mg).

HPLC/MS: m/z= 831 (M+1) @ t=4.56 min

MS: m/z= 831 (M+1)

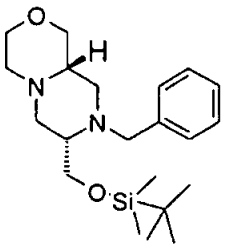
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.86 (s, 1 H) 7.63 - 7.81 (m, 2 H) 6.95 - 7.21 (m, 3 H) 6.64 (s, 1 H) 4.29 - 4.66 (m, 1 H) 3.99 - 4.24 (m, 1 H) 3.78 - 3.95 (m, 1 H) 3.59 - 3.81 (m, 1 H) 3.08 - 3.26 (m, 3 H) 2.91 - 3.16 (m, 3 H) 2.63 - 2.87 (m, 1 H) 2.48 (s, 3 H) 2.37 - 2.60 (m, 2 H) 2.08 - 2.33 (m, 1 H) 2.09 (s, 3 H) 1.37 (s, 6 H) 0.77 (s, 9 H) 0.01 (s, 6 H)

Description 125:
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*R*,9a*S or 9aR*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D125- Diastereoisomer 2)



To a solution of (7*R*,9a*S* or 9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]thiazine 2,2-dioxide (D123, 120 mg, 0.36 mmol) in 2.2 ml of toluene were added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (147 mg, 0.28 mmol), bis-tri–tert-butylphosphine palladium (29 mg), hexadecyltrimetylammonium chloride (18 μL of a 25% aqueous solution) and sodium hydroxide solution (36 μL of a 50% aqueous solution). The reaction mixture was degassed by freeze-pump-thaw cycles and it was stirred at 90°C for 5 hrs. Then further bis-tri–tert-butylphosphine palladium (29 mg) was added and the reaction mixture was stirred at 90°C for one more hour and was left in freezer overnight.
EtOAc and sat. $NaHCO_3$ aq. were added to the reaction mixture and the aqueous phase was extracted with EtOAc (x3). The combined organic phases were dried and evaporated to dryness. The crude was purified by chromatography (silica, cyclohexane:EtOAc 7:3 to 0:1) to give the title compound as a white solid (127.4 mg, y=55%).
MS: m/z= 831 (M+1)
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.86 (s, 1 H) 7.60 - 7.82 (m, 2 H) 7.16 (d, 1 H) 6.98 - 7.14 (m, 2 H) 6.67 (s, 1 H) 4.36 - 4.54 (m, 1 H) 3.91 - 4.12 (m, 1 H) 3.80 - 3.94 (m, 1 H) 3.58 - 3.73 (m, 1 H) 3.08 - 3.47 (m, 5 H) 2.87 - 3.00 (m, 1 H) 2.72 - 2.82 (m, 1 H) 2.42 - 2.67 (m, 6 H) 2.13 – 2.25 (m, 5 H) 1.26 – 1.54 (m, 4 H) 0.78 (s, 9 H) 0.00 (s, 6 H)

Description 126:
(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D126)



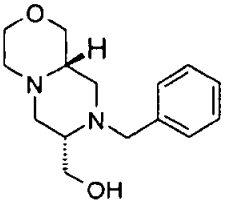
To a solution of (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D 22, 200 mg, 0.7 mmol) in dichloroethane (3 ml) were added under N_2, at r.t., PhCHO (0.142 ml, 1.4 mmol) and AcOH (79 µl, 1.4 mmol) and the reaction mixture was stirred for 30 mins. Sodium triacetoxyborohydride (295 mg, 1.4 mmol) was added and the reaction mixture was stirred for 3.5 hrs.

$NaHCO_3$ aq. was added to the reaction mixture and the two phases were separated. The aqueous phase was extracted with dichloromethane (3X) and the combined organic phases were dried and evaporated to dryness. The crude was purified by SCX and by chromatography (silica, CH_2Cl_2: 2M NH_3 in MeOH 1:0 to 95:5) to give 276 mg of the title compound as a colourless oil (276 mg, y=quantitative)

UPLC/MS: m/z= 377 (M+1) @ t=0.69 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 7.27 - 7.32 (m, 4 H) 7.18 - 7.24 (m, 1 H) 3.94 (t, 1 H) 3.83 (d, 1 H) 3.78 - 3.89 (m, 1 H) 3.68 - 3.75 (m, 1 H) 3.65 (d, 1 H) 3.42 - 3.54 (m, 2 H) 3.02 (t, 1 H) 2.74 (dd, 2 H) 2.45 - 2.50 (m, 1 H) 2.18 - 2.32 (m, 3 H) 2.08 - 2.18 (m, 2 H) 0.84 (s, 9 H) 0.02 (s, 3 H) 0.00 (s, 3 H)

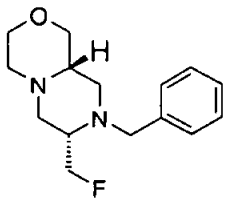
Description 127:
[(7*S*,9a*S*)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazin-7-yl]methanol (D127)



To a solution of (7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D126, 276 mg, 0.73 mmol) in MeOH (24 ml), cooled to 0°C, was added dropwise 12 N HCl (1.4 mL). The reaction mixture was stirred for 2 hrs at r.t., then it was put in the freezer for 12 hrs. The reaction mixture was warmed-up to r.t., further HCl was added (0.7 ml) and the reaction mixture was stirred for 2 more hrs. The mixture was filtered on a SCX

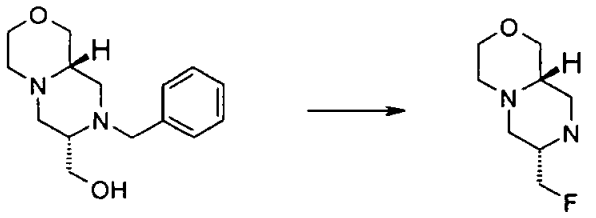
cartridge washing with methanol and then with 2M methanolic ammonia. The fractions eluted with ammonia were combined and evaporated to dryness to give the title compound as a colourless oil (150 mg, y=78%).
UPLC/MS: m/z= 263 (M+1) @ t=0.41 min
1H NMR (500 MHz, DMSO-d_6) δ ppm 7.26 - 7.33 (m, 4 H) 7.19 - 7.24 (m, 1 H) 4.42 (br. s., 1 H) 3.81 (d, 1 H) 3.74 - 3.83 (m, 2 H) 3.60 - 3.72 (m, 2 H) 3.43 - 3.52 (m, 2 H) 3.02 (t, 1 H) 2.78 (d, 1 H) 2.64 - 2.72 (m, 1 H) 2.53 (dd, 1 H) 2.18 - 2.29 (m, 3 H) 2.08 - 2.17 (m, 2 H)

Description 128: (7*S*,9a*S*)-7-(fluoromethyl)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D128)



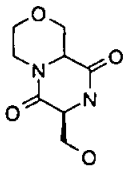
To a solution of [(7*S*,9a*S*)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazin-7-yl]methanol (D127, 125 mg, 0.477 mmol) in dichloromethane (5 ml), cooled to -78°C, was added DAST (0.187 ml, 1.431 mmol) dropwise and the reaction mixture was stirred for 16 hrs allowing the temperature to increase to r.t..
Water was added to the reaction mixture and the two phases were separated. The aqueous phase was extracted with dichloromethane (3X) and the combined organic phases were dried and evaporated to dryness. The crude was purified by chromatography (silica, CH_2Cl_2:MeOH 1:0 to 96:4) to give the title compound (106 mg).
MS: m/z= 265 (M+1)
UPLC/MS: m/z= 265 (M+1) @ t=0.47 min
1H NMR (500 MHz, DMSO-d_6) δ ppm 7.26 - 7.34 (m, 4 H) 7.19 - 7.26 (m, 1 H) 4.82 - 4.99 (m, 1 H) 4.59 - 4.76 (m, 1 H) 3.85 (d, 1 H) 3.70 (dd, 1 H) 3.63 (d, 1 H) 3.50 (dd, 1 H) 3.43 - 3.51 (m, 1 H) 3.02 - 3.09 (m, 1 H) 3.03 (t, 1 H) 2.68 (d, 1 H) 2.54 (d, 1 H) 2.29 - 2.36 (m, 2 H) 2.24 (t, 1 H) 2.08 - 2.16 (m, 2 H)

Description 129: (7*S*,9a*S*)-7-(fluoromethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D129)



To a solution of (7*S*,9a*S*)-7-(fluoromethyl)-8-(phenylmethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D128, 30 mg, 0.11 mmol) in AcOH (30 ml) was added Pd-black (12 mg, 0.11 mmol) and the reaction mixture was stirred under a H_2 atmosphere (5 atm.) for 1.5 hrs. The reaction mixture was filtered on a SCX cartridge washing with methanol and then with 2M methanolic ammonia. The fractions eluted with ammonia were combined and evaporated to dryness. The crude was purified by chromatography (silica, CH_2Cl_2:MeOH 1:0 to 8:2) to give the title compound (14.9 mg, y=78%).
1H NMR (400 MHz, DMSO-d_6) δ ppm 4.55 - 4.65 (m, 1 H) 4.42 - 4.53 (m, 1 H) 3.65 (dd, 1 H) 3.38 - 3.53 (m, 2 H) 2.99 (t, 1 H) 2.93 - 3.01 (m, 1 H) 2.58 (dd, 1 H) 2.42 - 2.45 (m, 1 H) 2.37 (dd, 1 H) 2.28 - 2.37 (m, 1 H) 2.12 - 2.20 (m, 1 H) 2.02 - 2.11 (m, 1 H) 1.92 - 2.00 (m, 1 H)
The whole ROESY cross peak pattern is in accordance with a *syn* relative stereochemistry.

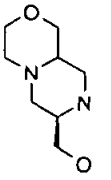
Description 130: (7*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione (D130)



N-Boc-3-morpholinecarboxylic acid (1.038 g, 4.49 mmol) was suspended in anhydrous dichloromethane (20mL). To it was added EDC (1.3g, 6.78 mmol) and HOBt (607 mg, 4.49 mmol) and stirred for 30 minutes at R.T., at which time complete dissolution of the starting material was observed. A solution of L-Ser-Methylester hydrochloride (1.10 g, 17.07 mmol), and DIPEA (1.23 mL, 7.07 mmol) in dry dichloromethane (10 mL) was added. The resulting mixture was stirred overnight. Diluted with dichloromethane (50mL), washed with sat $NaHCO_3$ solution (2 x 50mL) and brine (50 mL). Dried (Na_2SO_4) and solvent removed under reduced pressure to afford a crude used in the next step.
It was dissolved in 20 mL of dichloromethane and treated with 10 mL of TFA. The reaction was stopped after 4 h. The mixture was passed through a SCX column. The basic components were eluted with 1M methanolic ammonia. The solvent was removed leaving an oily residue, which was re-dissolved in MeOH and heated to remove the solvent. A precipitate formed, which was collected by filtration as a

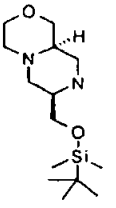
white solid, corresponding to the title compound, with a 70:30 diastereomeric excess.
MS (direct): m/z= 201 (M+1)
1H NMR (500 MHz, DMSO-d_6) d ppm 8.15 (br. s., 1 H) 5.16 (t, 1 H) 4.22 (dd, 1 H) 4.08 - 4.13 (m, 1 H) 4.00 (dd, 1 H) 3.84 - 3.88 (m, 1 H) 3.77 - 3.83 (m, 1 H) 3.71 - 3.80 (m, 1 H) 3.44 - 3.51 (m, 1 H) 3.41 (t, 1 H) 3.30 (t, 1 H) 2.77 (td, 1 H) (mixture of diastereoisomers, ratio about 70:30)

Description 131: (7*R*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D131)



(7*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazine-6,9-dione (D130, 151 mg, 0.75 mmol) was suspended in 1M borane THF complex solution (7.5 mL) and heated at reflux for 24 hours. Checked by MS, which showed only the product at m/z= 173 (M+1). The reaction was cooled to 0°C, MeOH (5 mL) added dropwise followed by conc.HCl solution (1 mL). The resulting mixture was heated at 50°C for 4 hours. The solvent was removed and the residue loaded on a SCX column, washed with MeOH before eluting the compound with 1M NH_3 in MeOH. Solvent evaporated under reduced pressure to afford the title compound as a colourless oil (125 mg).
1H NMR (500 MHz, DMSO-d_6) d ppm 4.43 (t, 1 H) 3.68 (dd, 1 H) 3.62 (t, 1 H) 3.40 - 3.58 (m, 4 H) 3.02 (t, 1 H) 2.66 - 2.74 (m, 1 H) 2.62 (d, 1 H) 2.42 - 2.51 (m, 1 H) 2.31 - 2.39 (m, 1 H) 2.15 (dd, 1 H) 2.09 (td, 1 H) 1.92 - 2.03 (m, 1 H)

Description 132: (7*R*,9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D132)

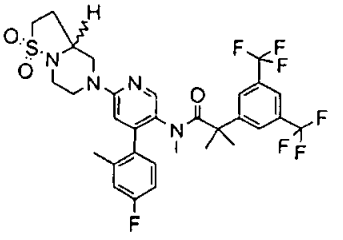


(7*R*)-octahydropyrazino[2,1-*c*][1,4]oxazin-7-ylmethanol (D131, 93 mg, 0.54 mmol, a sample recovered from a failed attempt at silylating the preparation of Dnn) was dissolved in dry dichloromethane (2 mL) and treated with Et_3N (0.15 mL, 1.08

mmol), and TBDMS-Cl (122 mg, 0.81 mmol). The resulting reaction mixture was stirred overnight at R.T. It was checked by direct MS, showing no starting material, replaced by the expected peak at m/z= 287 (M+1 of the product). It was diluted with dichloromethane (20 mL) and washed with sat $NaHCO_3$ solution (2 x 20mL), dried (Na_2SO_4) and the solvent was removed. The residue was purified by flash chromatography (silica, dichloromethane to dichloromethane : MeOH 90:10), leaving the product as a clear oil.
MS (direct): m/z= 287 (M+1)
1H NMR (500 MHz, DMSO-d_6) d ppm 7.48 (br. s., 1 H) 7.07 (br. s., 1 H) 3.82 (dd, 1 H) 3.75 (dd, 1 H) 3.69 (dd, 1 H) 3.55 (dd, 1 H) 3.42 - 3.49 (m, 1 H) 3.03 (t, 1 H) 2.86 - 2.93 (m, 1 H) 2.68 (dd, 1 H) 2.50 - 2.54 (m, 1 H) 2.33 - 2.46 (m, 2 H) 2.21 (dd, 1 H) 2.04 - 2.16 (m, 2 H) 0.86 (s, 9 H) 0.04 (s, 6 H) – protonated form.

Example 1

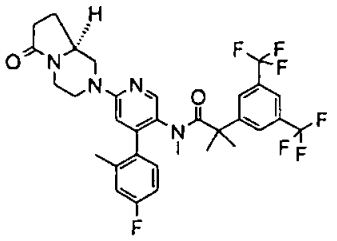
2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-(1,1-dioxidohexahydro-5*H*-isothiazolo[2,3-*a*]pyrazin-5-yl)-4-(4-fluoro-2-methylphenyl)pyridin-3-yl]-*N*,2-dimethylpropanamide (E1)



A 8 ml sealed vial was charged with 100 mg (0.187 mmol) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 98 mg (0.561mmol) of hexahydro-2*H*-isothiazolo[2,3-*a*] pyrazine 1,1-dioxide (D10), 52 mg (0.374 mmol) of potassium carbonate; the reagents were dissolved in 0.8 ml of DMSO. The reaction mixture was heated at 180°C for 36-48hrs and then added to a saturated NH_4Cl solution and back extracted with dichloromethane; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to cyclohexane/ethyl acetate 1:1 and affording 44 mg (0.065 mmol) of the title compound as pale yellow solid.
MS (ES/+): 673 $[M+H]^+$
NMR (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.08-6.85 (m, 3H); 6.53 (s, 1H); 4.81-4.53 (m, 1H); 4.35-4.09 (m, 1H); 3.53-3.50 (m, 1H); 3.38-3.25 (m, 1H); 3.16-3.09 (m, 1H); 2.96 (t, 1H); 2.83 (t, 1H); 2.70-1.98 (m, 10H); 1.79-1.47 (m, 3H); 1.46-1.33 (s, 3H).

Example 2

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*S*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E2)



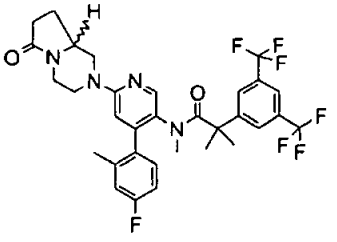
A 8 ml sealed vial was charged with 100 mg (0.187 mmol) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 78.6 mg (0.561 mmol) of (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (WO 2003/066635), 52 mg (0.374 mmol) of potassium carbonate; the reagents were dissolved in 0.8 ml of DMSO. The reaction mixture was heated at 180°C for 36-48hrs and then added to a saturated NH_4Cl solution and back extracted with dichloromethane; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 52 mg of the title compound as pale yellow solid.

MS (ES/+): 637 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.05-6.87 (m, 3H); 6.52 (s, 1H); 4.67-4.52 (m, 1H); 4.32-4.19 (m, 1H); 4.14-4.10 (d, 1H); 3.77-3.64 (m, 1H); 3.02-2.84 (m, 2H); 2.61 (t, 1H); 2.48-2.44 (dd, 2H); 2.41-2.33 (s, 3H); 2.30-2.22 (m, 1H); 2.13 (s, 3H); 1.79-1.65 (m, 1H); 1.53 (s, 3H); 1.38 (s, 3H).

Example 3

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E3)



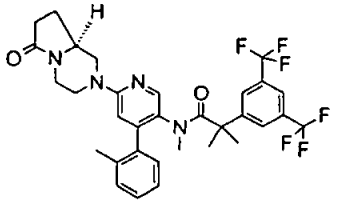
A 8 ml sealed vial was charged with 100 mg (0.187 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 78.6 mg (0.561mmol) of hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (WO 2003/066635), 52 mg (0.374 mmol) of potassium carbonate; the reagents were dissolved in 0.8ml of DMSO. The reaction mixture was heated at 180°C for 36-48hrs and then added to a saturated NH_4Cl solution and back extracted with dichloromethane; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 71mg of the title compound as pale yellow solid.

MS (ES/+): 637 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.05-6.87 (m, 3H); 6.52 (s, 1H); 4.67-4.52 (m, 1H); 4.32-4.19 (m, 1H); 4.14-4.10 (d, 1H); 3.77-3.64 (m, 1H); 3.02-2.84 (m, 2H); 2.61 (t, 1H); 2.48-2.44 (dd, 2H); 2.41-2.33 (s, 3H); 2.30-2.22 (m, 1H); 2.13 (s, 3H); 1.79-1.65 (m, 1H); 1.53 (s, 3H); 1.38 (s, 3H)

Example 4

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*,2-dimethyl-*N*-{4-(2-methylphenyl)-6-[(8a*S*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}propanamide (E4)



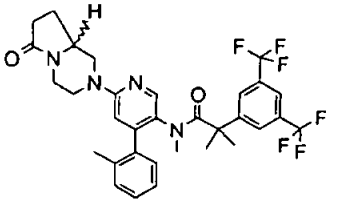
A 8 ml sealed vial was charged with 100 mg (0.161 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 67 mg (0.483mmol) of (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (WO 2003/066635), 44.5 mg (0.322mmol) of potassium carbonate; the reagents were dissolved in 0.8 ml of DMSO. The reaction mixture was heated at 180°C for 36-48hrs and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 56 mg of the title compound as pale yellow solid.

MS (ES/+): 619 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.07-8.00 (m, 1H); 7.81-7.77 (m, 1H); 7.73-7.63 (m, 2H); 7.37-7.21 (m, 4H); 6.61-6.56 (m, 1H); 4.68-4.54 (m, 1H); 4.33-4.19 (m, 1H); 4.18-4.08 (d, 1H); 3.78-3.67 (m, 1H); 3.04-2.85 (m, 2H); 2.69-2.54 (t, 1H); 2.53-2.42 9dd, 1H); 2.42-2.33 (m, 3H); 2.33-2.23 (m, 1H); 2.21-2.10 (m, 3H); 1.78.-1.66 (m, 1H); 1.57-1.48 (m, 3H); 1.42-1.32 (m, 3H).

Example 5

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*,2-dimethyl-*N*-[4-(2-methylphenyl)-6-(6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-3-pyridinyl]propanamide (E5)



A 8 ml sealed vial was charged with 100 mg (0.161 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 67 mg (0.483 mmol) of hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (WO 2003/066635), 44.5 mg (0.322 mmol) of potassium carbonate;

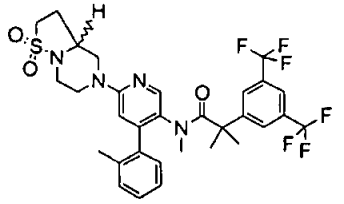
the reagents were dissolved in 0.8ml of DMSO. The reaction mixture was heated at 180°C for 36-48hrs and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 45 mg of the title compound as pale yellow solid.

MS (ES/+): 619 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.07-8.00 (m, 1H); 7.81-7.77 (m, 1H); 7.73-7.63 (m, 2H); 7.37-7.21 (m, 4H); 6.61-6.56 (m, 1H); 4.68-4.54 (m, 1H); 4.33-4.19 (m, 1H); 4.18-4.08 (d, 1H); 3.78-3.67 (m, 1H); 3.04-2.85 (m, 2H); 2.69-2.54 (t, 1H); 2.53-2.42 9dd, 1H); 2.42-2.33 (m, 3H); 2.33-2.23 (m, 1H); 2.21-2.10 (m, 3H); 1.78.-1.66 (m, 1H); 1.57-1.48 (m, 3H); 1.42-1.32 (m, 3H).

Example 6

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-(1,1-dioxidohexahydro-5*H*-isothiazolo[2,3-*a*]pyrazin-5-yl)-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E6)



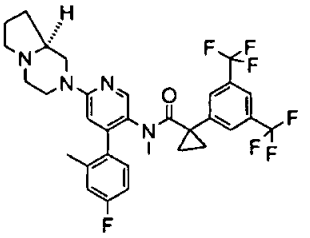
The title compound was prepared starting from 100 mg (0.161 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 85 mg (0.483 mmol) of hexahydro-2*H*-isothiazolo[2,3-*a*] pyrazine 1,1-dioxide (D10), 44.5 mg (0.322mmol) of potassium carbonate; the reagents were dissolved in 0.8 ml of DMSO . The reaction mixture was heated at 180°C for 36-48hrs and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to cyclohexane/ethyl acetate 1:1 and affording 80mg of the title compound as pale yellow solid.

MS (ES/+): 655 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.08-8.00 (m, 1H), 7.82-7.76 (m, 1H); 7.71-7.64 (m, 2H); 7.37-7.22 (m, 4H); 6.62-6.57 (m, 1H); 4.80-4.60 (m, 1H); 4.36-4.12 (m, 1H); 3.58- 3.46 (m, 1H); 3.39-3.27 (m, 1H); 3.25-3.16 (m, 1H); 3.17-3.08 (t, 1H); 3.05-2.91 (t, 1H); 2.90-2.78 (t, 1H); 2.54-2.44 (m, 3H); 2.44-2.31 (m, 2H); 2.20-2.12 (m, 3H); 2.31-2.01 (m, 1H); 1.58-1.50 (m, 3H); 1.44-1.31 (m, 3H)

Example 7

1-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*-methylcyclopropanecarboxamide (E7)



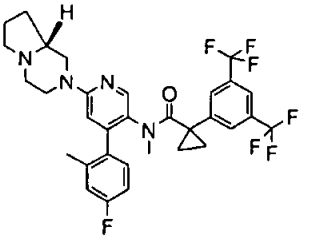
The title compound was prepared starting from 100 mg (0.188 mmoles) of 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]cyclopropanecarboxamide (D2), 70 mg (0.554mmol) of (8a*S*)-octahydropyrrolo[1,2-*a*]pyrazine, 52.2 mg (0.377 mmol) of potassium carbonate; the reagents were dissolved in 0.8ml of DMSO. The reaction mixture was heated at 150°C overnight and then added to a saturated NH_4Cl solution and back extracted with dichloromethane; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 1:1, to ethyl acetate 100%, affording 72 mg of the title compound as pale yellow solid.

MS (ES/+): 621 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 7.93-7.89 (s, 1H); 7.86-7.82 (s, 1H); 7.67-7.62 (s, 2H); 7.06-7.01 (d, 1H); 6.89-6.77 (m, 2H); 6.57-6.52 (m, 1H); 4.38-4.34 (d, 1H); 4.21-4.17 (d, 1H); 3.10-2.87 (m, 2H); 2.88-2.84 (s, 3H); 2.62-2.50 (m, 1H); 2.26-2.06 (m, 2H); 2.17-2.10 (s, 3H); 2.06-1.94 (s, 1H); 1,90-1.61 (m, 3H); 1.46-1.10 (m, 6H)

Example 8

1-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*-methylcyclopropanecarboxamide (E8)



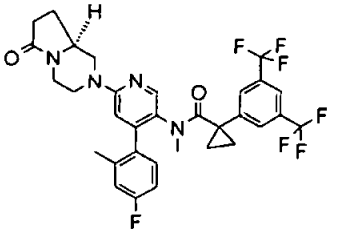
The title compound was prepared starting from 100 mg (0.188 mmoles) of 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]cyclopropanecarboxamide (D2), 70 mg (0.554mmol) of (8a*R*)-octahydropyrrolo[1,2-*a*]pyrazine, 52.2 mg (0.377 mmol) of potassium carbonate; the reagents were dissolved in 0.8 ml of DMSO. The reaction mixture was heated at 150°C overnight and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 1:1, to ethyl acetate 100% and affording 70 mg of the title compound as pale yellow solid.

MS (ES/+): 621 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 7.93-7.89 (s, 1H); 7.86-7.82 (s, 1H); 7.67-7.62 (s, 2H); 7.06-7.01 (d, 1H); 6.89-6.77 (m, 2H); 6.57-6.52 (m, 1H); 4.38-4.34 (d, 1H); 4.21-4.17 (d, 1H); 3.10-2.87 (m, 2H); 2.88-2.84 (s, 3H); 2.62-2.50 (m, 1H); 2.26-2.06 (m, 2H); 2.17-2.10 (s, 3H); 2.06-1.94 (s, 1H); 1,90-1.61 (m, 3H); 1.46-1.10 (m, 6H)

Example 9

1-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*S*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*-methylcyclopropanecarboxamide (E9)



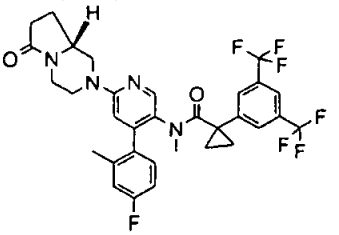
The title compound was prepared starting from 50 mg (0.094 mmoles) of 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]cyclopropanecarboxamide (D2), 39 mg (0.278mmol) of (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (WO 2003/066635), 26.2 mg (0.189mmol) of potassium carbonate; the reagents were dissolved in 0.4ml of DMSO . The reaction mixture was heated at 150°C overnight and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 1:1, to ethyl acetate 100% and affording 26 mg of the title compound as pale yellow solid.

MS (ES/+): 635 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.03-7.99 (m, 1H); 7.99-7.95 (m, 1H); 7.74-7.69 (m, 2H); 7.20-7.10 (m, 1H); 7.06-6.93 (m, 1H); 6.92-6.83 (m, 1H); 6.81-6.74 (m, 1H); 4.55-4.47 (d, 1H); 4.44-4.37 (d, 1H); 3.88-3.78 (d, 1H); 3.60-3.50 (d, 1H); 2.84-2.66 (m, 4H); 2.59-2.38 (m, 2H); 2.32-2.18 (m, 2H); 2.15-2.09 (m, 3H); 2.17-2.06 (m, 1H); 1.64-1.53 (m, 1H); 1.32-1.19 (m, 2H); 1.15-1.02 (m, 1H); 0.96-0.78 (1, H).

Example 10

1-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*-methylcyclopropanecarboxamide (E10)



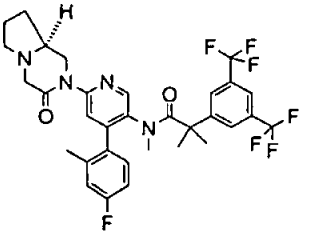
The title compound was prepared from 50 mg (0.094 mmoles) of 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]cyclopropanecarboxamide (D2), 39 mg (0.278 mmol) of (8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (WO 2003/066635), 26.2 mg (0.189 mmol) of potassium carbonate; the reagents were dissolved in 0.4ml of DMSO . The reaction mixture was heated at 150°C overnight and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 1:1, to ethyl acetate 100% and affording 12 mg of the title compound as pale yellow solid.

MS (ES/+): 635 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.03-7.99 (m, 1H); 7.99-7.95 (m, 1H); 7.74-7.69 (m, 2H); 7.20-7.10 (m, 1H); 7.06-6.93 (m, 1H); 6.92-6.83 (m, 1H); 6.81-6.74 (m, 1H); 4.55-4.47 (d, 1H); 4.44-4.37 (d, 1H); 3.88-3.78 (d, 1H); 3.60-3.50 (d, 1H); 2.84-2.66 (m, 4H); 2.59-2.38 (m, 2H); 2.32-2.18 (m, 2H); 2.15-2.09 (m, 3H); 2.17-2.06 (m, 1H); 1.64-1.53 (m, 1H); 1.32-1.19 (m, 2H); 1.15-1.02 (m, 1H); 0.96-0.78 (1, H).

Example 11

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*S*)-3-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E11)



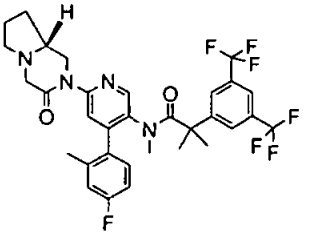
The title compound was prepared starting from 100 mg (0.187 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 79 mg (0.563 mmol) of (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (D12), 72mg of copper iodide (0.378mmol), 40µl (0.375 mmol) of *N*,*N*-dimethylmethanediamine, 112.4 mg (0.375 mmol) of cesium carbonate; the reagents were dissolved in 4 ml of dioxane and heated at 80°C for 4h and then at 120 °C overnight. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 54 mg of the title compound as pale yellow solid.

MS (ES/+): 637 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.39-8.23 (br. s, 1H), 8.09-7.97 (s, 1H), 7.87-7.64 (m, 3H), 7.21 (d, 1H), 7.17-7.06 (m, 2H), 4.62-4.15 (m, 2H), 4.09-3.65 (m, 2H), 3.19-3.00 (m, 1H), 2.87-2.53 (m, 2H), 2.42-2.24 (m, 1H), 2.20-2.04 (m, 6H), 2.00-1.88 (m, 1H), 1.88-1.76 (m, 1H), 1.75-1.59 (m, 1H), 1.59-1.47 (m, 1H), 1.46-1.23 (m, 6H)

Example 12

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-3-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E12)



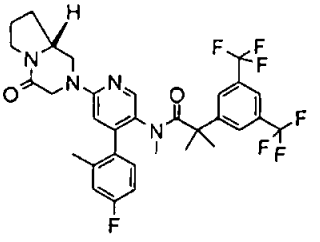
The title compound was prepared starting from 100 mg (0.187 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 79mg (0.563 mmol) of (8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (D14), 72 mg of copper iodide (0.378mmol), 40µl (0.375mmol) of *N*,*N*-dimethylmethanediamine, 112.4 mg (0.375mmol) of cesium carbonate; the reagents were dissolved in 4 ml of dioxane and heated at 80°C for 4h and then at 120 °C overnight. The crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 60mg of the title compound as pale yellow solid.

MS (ES/+): 637 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.39-8.23 (br. s, 1H), 8.09-7.97 (s, 1H), 7.87-7.64 (m, 3H), 7.21 (d, 1H), 7.17-7.06 (m, 2H), 4.62-4.15 (m, 2H), 4.09-3.65 (m, 2H), 3.19-3.00 (m, 1H), 2.87-2.53 (m, 2H), 2.42-2.24 (m, 1H), 2.20-2.04 (m, 6H), 2.00-1.88 (m, 1H), 1.88-1.76 (m, 1H), 1.75-1.59 (m, 1H), 1.59-1.47 (m, 1H), 1.46-1.23 (m, 6H).

Example 13

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-4-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E13)



The title compound was prepared starting from 250 mg (0.47 mmole) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), (8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one (D4), 164.4 mg (1.17 mmol), 130mg of potassium carbonate (0.94 mmol); the reagents were dissolved in 1.5 ml of DMSO. The reaction mixture was heated at 150°C overnight and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient cyclohexane/ethyl

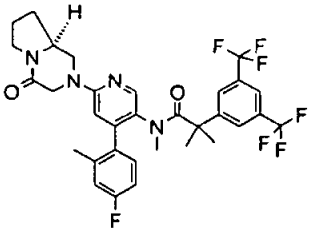
acetate 9:1, to ethyl acetate 100% and affording 115 mg of the title compound as pale yellow solid.

MS (ES/+): 637 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.95-7.89 (s, 1H); 7.80-7.69 (br.s, 2H); 7.74-7.64 (br.s, 1H); 7.19-7.11 (d, 1H); 6.71-6.65 (s, 1H); 4.77-4.64 (d, 1H); 4.45-4.32 (d, 1H); 3.72-3.59 (m, 1H); 3.52-3.41 (dd, 1H); 3.39-3.31 (m, 1H); 2.83-2.73 (t, 1H); 2.60-2.50 (m, 1H); 2.31-2.17 (s, 3H); 2.21-2.15 (m, 1H); 2.15-2.05 (s, 3H); 1.97-1.88 (m, 1H); 1.82-1.71 (m, 1H); 1.71-1.58 (m, 1H); 1.55-1.42 (s, 3H); 1.41-1.27 (s, 3H).

Example 14

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-4-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E14)



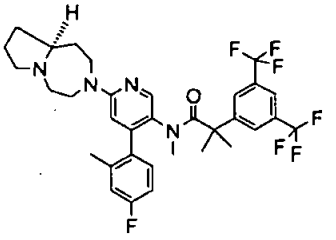
The title compound was prepared starting from 135 mg (0.253 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 70 mg (0.5 mmol) of (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one (EP 300189), 70 mg (0.5 mmol) of potassium carbonate; the reagents were dissolved in 0.8 ml of DMSO. The reaction mixture was heated at 150°C overnight and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 24 mg of the title compound as pale yellow solid.

MS (ES/+): 637 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.95-7.89 (s, 1H); 7.80-7.69 (br.s, 2H); 7.74-7.64 (br.s, 1H); 7.19-7.11 (d, 1H); 6.71-6.65 (s, 1H); 4.77-4.64 (d, 1H); 4.45-4.32 (d, 1H); 3.72-3.59 (m, 1H); 3.52-3.41 (dd, 1H); 3.39-3.31 (m, 1H); 2.83-2.73 (t, 1H); 2.60-2.50 (m, 1H); 2.31-2.17 (s, 3H); 2.21-2.15 (m, 1H); 2.15-2.05 (s, 3H); 1.97-1.88 (m, 1H); 1.82-1.71 (m, 1H); 1.71-1.58 (m, 1H); 1.55-1.42 (s, 3H); 1.41-1.27 (s, 3H).

Example 15

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*S*)-octahydro-3*H*-pyrrolo[1,2-*d*][1,4]diazepin-3-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E15)



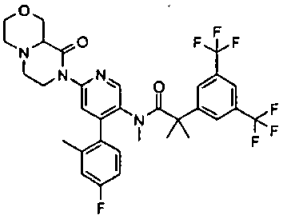
A 8 ml sealed vial was charged with 60 mg (0.112mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 47 mg (0.335mmol) of (9a*S*)-octahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepine (D6), 31mg of potassium carbonate (0.224 mmol); the reagents were dissolved in 0.5 ml of DMSO. The reaction mixture was heated at 150°C overnight and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 1:1, to ethyl acetate 100% and affording 32mg of the title compound as pale yellow solid.

MS (ES/+): 637 $[M+H]^+$

NMR (DMSO-d_6): 8.02 (s, 1H), 7.93-7.82 (br.s, 1H), 7.79-7.70 (br.s, 2H), 7.73-7.64 (br.s, 1H), 7.15 (t, 1H), 7.13-7.03 (br. s, 1H), 6.66-6.52(br. s, 1H), 4.28-3.98 (br. s, 1H0, 3.80-3.51 (br. s, 4H), 3.51-3.39 (br. s, 1H), 3.26-3.03 (br. s, 1H), 2.60-2.45 (br. s, 1H), 2.22 (s, 3H), 2.12 (s, 3H), 2.07-1.77 (br. s, 3H), 1.48 (s, 3H), 1.55-1.24 (m, 2H), 1.33 (s, 3H), 1.26-1.14 (m, 1H).

Example 16

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(9-oxohexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E16)



A 8 ml sealed vial was charged with 150 mg (0.281 mmol) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 120 mg (0.768 mmol) of hexahydropyrazino[2,1-*c*][1,4]oxazin-9(6*H*)-one (D7), 60 µL (0.563 mmol) of N,N'-dimethylethylenediamine, 110 mg (0.578 mmol) of copper iodide, 183 mg (0.562 mmol) of cesium carbonate; the reagents were dissolved in 4.5 ml of dioxane. The reaction mixture is stirred overnight at 150°C. The crude was purified by chromatography (silica, cyclohexane/EtOAc 90/10 – 30/70) affording the title compound as a white solid: 73 mg, 0.111 mmol, 40% yield.

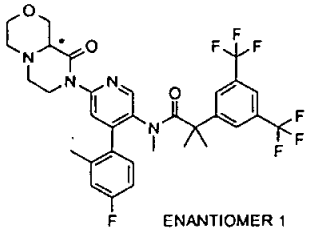
Rf: 0.55 (EtOAc)

MS (ES/+): 653 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.34-8.26 (s, 1H); 8.06-7.99 (s, 1H); 7.81-7.69 (br.s, 2H); 7.72-7.65 (br.s, 1H); 7.21-7.15 (d, 1H); 7.15-7.08 (s, 1H); 4.13-4.05 (dd, 1H); 4.03-3..82 (br.s, 2H); 3.80-3.72 (dd, 1H); 3.54-3.46 (dd, 1H); 3.40-3.31 (m, 1H); 3.14-3.06 (dd, 1H); 3.02-2.95 (dd, 1H); 2.86-2.80 (dd, 1H); 2.72-2.61 (m, 2H); 2.36-2.28 (t, 1H); 2.39-2.22 (br.s, 3H); 2.19-2.04 (br.s, 3H); 1.61-1.44 (br.s, 3H); 1.45-1.30 (br.s,3H).

Example 17

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(9-oxohexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E17) ENANTIOMER 1 of E16



ENANTIOMER 1

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(9-oxohexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E16; 42 mg) was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled 1, of unknown but single stereochemistry was isolated using the following conditions (20 mg, 100%e.e.)

Preparative conditions:

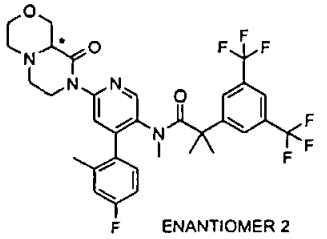
Amount supplied	42 mg
Chiral Column	CHIRALCEL OD, (25 x 2) cm
Mobile phase	n-Hexane/2-propanol 94/6 % v/v
Flow rate	18 ml/min
Detection	UV at 225 nm
Run Time	17 min

MS (ES/+): 653 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.34-8.26 (s, 1H); 8.06-7.99 (s, 1H); 7.81-7.69 (br.s, 2H); 7.72-7.65 (br.s, 1H); 7.21-7.15 (d, 1H); 7.15-7.08 (s, 1H); 4.13-4.05 (dd, 1H); 4.03-3..82 (br.s, 2H); 3.80-3.72 (dd, 1H); 3.54-3.46 (dd, 1H); 3.40-3.31 (m, 1H); 3.14-3.06 (dd, 1H); 3.02-2.95 (dd, 1H); 2.86-2.80 (dd, 1H); 2.72-2.61 (m, 2H); 2.36-2.28 (t, 1H); 2.39-2.22 (br.s, 3H); 2.19-2.04 (br.s, 3H); 1.61-1.44 (br.s, 3H); 1.45-1.30 (br.s,3H) .

Example 18

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(9-oxohexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E18) ENANTIOMER 2 of E16



ENANTIOMER 2

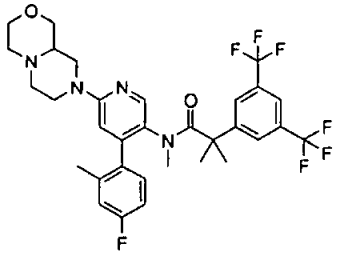
The title compound was isolated using the same conditions as E17, obtaining 17 mg, 100% e.e.

MS (ES/+): 653 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.34-8.26 (s, 1H); 8.06-7.99 (s, 1H); 7.81-7.69 (br.s, 2H); 7.72-7.65 (br.s, 1H); 7.21-7.15 (d, 1H); 7.15-7.08 (s, 1H); 4.13-4.05 (dd, 1H); 4.03-3..82 (br.s, 2H); 3.80-3.72 (dd, 1H); 3.54-3.46 (dd, 1H); 3.40-3.31 (m, 1H); 3.14-3.06 (dd, 1H); 3.02-2.95 (dd, 1H); 2.86-2.80 (dd, 1H); 2.72-2.61 (m, 2H); 2.36-2.28 (t, 1H); 2.39-2.22 (br.s, 3H); 2.19-2.04 (br.s, 3H); 1.61-1.44 (br.s, 3H); 1.45-1.30 (br.s,3H).

Example 19

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E19)



A 8 ml sealed vial was charged with 124 mg (0.233 mmol) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577); 83 mg (0.584 mmol) of octahydropyrazino[2,1-*c*][1,4]oxazine (EP 472826), 90 mg (0.701 mmol) of potassium carbonate; the reagents were dissolved in 0.5ml of DMSO. The crude product was purified by flash chromatography (silica, cyclohexane/EtOAc 90/10 – 30/70) affording the title compound as a white solid 85 mg (0.133 mmol).

Rf: 0.4 (EtOAc)

MS (ES/+): 639 $[M+H]^+$.

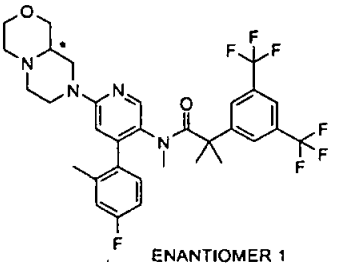
NMR (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.91-7.85 (s, 1H); 7.79-7.68 (m, 2H); 7.73-7.65 (br.s, 1H); 7.18-7.12 (d, 1H); 7.13-7.06 (br.s,1H); 6.73-6.64 (s, 1H); 4.29-4.18 (d, 1H); 4.13-4.03 (d, 1H); 3.78-3.68 (t, 2H); 3.56-3.48 (t, 1H); 3.18-3.09 (t, 1H); 2.92-2.80 (t, 1H); 2.82-

2.74 (d, 1H); 2.70-2.62 (d, 1H); 2.44-2.34 (t, 1H); 2.21-2.15 (s, 3H); 2.28-2.06 (m, 3H); 2.14-2.07 (s, 3H); 1.55-1.41 (s, 3H); 1.40-1.28 (s, 3H).

Example 20

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E20) ENANTIOMER 1 of E19

[[α]$_D$=1.8, c=1.0, MeOH]



ENANTIOMER 1

Example 19 (15 mg) was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled 1, of unknown but single stereochemistry was isolated using the following conditions (5 mg, 97.2%e.e.)

Preparative conditions:

Amount supplied	15 mg
Chiral Column	CHIRALCEL OD, (25 x 2) cm
Mobile phase	n-Hexane/2-propanol 94/6 % v/v
Flow rate	18 ml/min
Detection	UV at 225 nm
Run Time	17 min

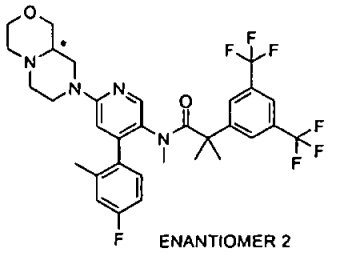
MS (ES/+): 639 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.91-7.85 (s, 1H); 7.79-7.68 (m, 2H); 7.73-7.65 (br.s, 1H); 7.18-7.12 (d, 1H); 7.13-7.06 (br.s,1H); 6.73-6.64 (s, 1H); 4.29-4.18 (d, 1H); 4.13-4.03 (d, 1H); 3.78-3.68 (t, 2H); 3.56-3.48 (t, 1H); 3.18-3.09 (t, 1H); 2.92-2.80 (t, 1H); 2.82-2.74 (d, 1H); 2.70-2.62 (d, 1H); 2.44-2.34 (t, 1H); 2.21-2.15 (s, 3H); 2.28-2.06 (m, 3H); 2.14-2.07 (s, 3H); 1.55-1.41 (s, 3H); 1.40-1.28 (s, 3H).

Example 21

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E21) ENANTIOMER 2 of E19

[[α]$_D$ =-1.0]



ENANTIOMER 2

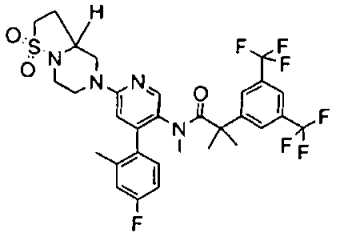
The title compound was isolated using the same conditions as E20, obtaining 5 mg, 99.8% e.e.

MS (ES/+): 639 $[M+H]^+$.

NMR (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.91-7.85 (s, 1H); 7.79-7.68 (m, 2H); 7.73-7.65 (br.s, 1H); 7.18-7.12 (d, 1H); 7.13-7.06 (br.s,1H); 6.73-6.64 (s, 1H); 4.29-4.18 (d, 1H); 4.13-4.03 (d, 1H); 3.78-3.68 (t, 2H); 3.56-3.48 (t, 1H); 3.18-3.09 (t, 1H); 2.92-2.80 (t, 1H); 2.82-2.74 (d, 1H); 2.70-2.62 (d, 1H); 2.44-2.34 (t, 1H); 2.21-2.15 (s, 3H); 2.28-2.06 (m, 3H); 2.14-2.07 (s, 3H); 1.55-1.41 (s, 3H); 1.40-1.28 (s, 3H).

Example 22

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-(1,1-dioxidohexahydro-5*H*-isothiazolo[2,3-*a*]pyrazin-5-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E22) ENANTIOMER 1 of E1



Preparative conditions:

Amount supplied 37 mg

Chiral Column	CHIRALPAK AD-H, (25 x 2) cm
Mobile phase	n-Hexane/Ethanol+ 0.1% isopropylamine 25/75 % v/v
Flow rate	15 ml/min
Detection	UV at 225 nm

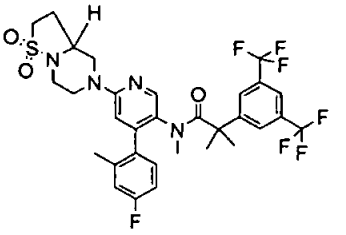
Isolated: 4 mg ; purity of enantiomer 1 resulted to be 100 %

MS (ES/+): 673 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.08-6.85 (m, 3H); 6.53 (s, 1H); 4.81-4.53 (m, 1H); 4.35-4.09 (m, 1H); 3.53-3.50 (m, 1H); 3.38-3.25 (m, 1H); 3.16-3.09 (m, 1H); 2.96 (t, 1H); 2.83 (t, 1H); 2.70-1.98 (m, 10H); 1.79-1.47 (m, 3H); 1.46-1.33 (s, 3H).

Example 23

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-(1,1-dioxidohexahydro-5*H*-isothiazolo[2,3-*a*]pyrazin-5-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E23) ENANTIOMER 2 of E1



Preparative conditions:

Chiral Column	CHIRALPAK AD-H, (25 x 2) cm
Mobile phase	n-Hexane/Ethanol+ 0.1% isopropylamine 25/75 % v/v
Flow rate	15 ml/min
Detection	UV at 225 nm

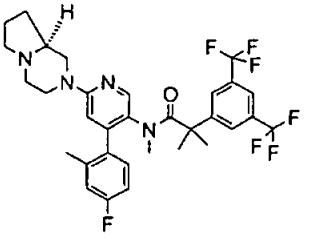
Isolated: 6 mg ;purity of enantiomer 2 was 98.8% by UV

MS (ES/+): 673 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.08-6.85 (m, 3H); 6.53 (s, 1H); 4.81-4.53 (m, 1H); 4.35-4.09 (m, 1H); 3.53-3.50 (m, 1H); 3.38-3.25 (m, 1H); 3.16-3.09 (m, 1H); 2.96 (t, 1H); 2.83 (t, 1H); 2.70-1.98 (m, 10H); 1.79-1.47 (m, 3H); 1.46-1.33 (s, 3H).

Example 24

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E24)



A 10 ml microwave tube was charged with 80 mg (0.150 mmol) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 47.4 mg (0.375mmol) of (8a*S*)-octahydropyrrolo[1,2-*a*]pyrazine, 62.2 mg (0.450mmol) of potassium carbonate; the reagents were dissolved in 0.6 ml of DMSO. The reaction mixture was irradiated in a microwave oven (180 °C, 300W) for 1 hour and then the crude is purified by a Mass Directed Preparative Instrument by Waters (System Fraction Lynx TM) performed on a X

Terra Prep MS C18 (30 x 150 mm; 10 µm) (mobile phase: from 99% [water +0.1% HCO2H] and 1% [CH_3CN +0.1% HCO_2H] to 100% [CH_3CN +0.1% HCO_2H] in 8 min and 30"; 100% [CH_3CN +0.1% HCO_2H] for 6 min; from 100% [CH_3CN +0.1% HCO_2H] to 99% [water +0.1% HCO_2H] and 1% [CH_3CN +0.1% HCO_2H] in 30"; 99% [water +0.1% HCO_2H] and 1% [CH_3CN +0.1% HCO_2H] for 12"); T=rt; flow rate= 40 ml/min; UV Detection :210-400 nm; MS Detection Mode: ES (+)/ ES (-) , Mass Range: 100-900] to afford 45mg of the target compound as pale yellow solid.

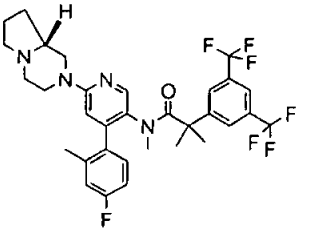
R_F = 0.2 (Ethyl Acetate)

MS (ES/+): 623 $[M+H]^+$

NMR ($CDCl_3$): δ (ppm) 8.00 (s, 1H), 7.78 (s, 1H), 7.71-7.60 (br. s, 2H), 7.27-7.22 (br. s, 1H), 7.05-6.85 (br. s, 2H), 6.52-6.45 (s, 1H), 4.63-3.98 (m, 2H), 3.74-2.94 (m, 4H), 2.42-2.29 (s, 3H), 2.67-1.86 (m, 3H), 2.17-2.07 (s, 3H), 1.56-1.48 (s, 3H), 1.81-1.12 (m, 4H), 1.41-1.33 (s, 3H).

Example 25

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E25)



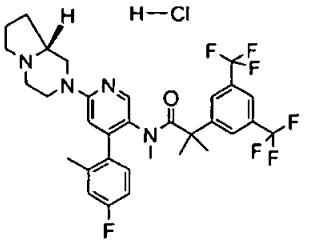
The title compound was prepared starting from 100 mg (0.187 mmole) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 70mg (0.554mmol) of (8a*R*)-octahydropyrrolo[1,2-*a*]pyrazine, 52.2 mg of potassium carbonate (0.377 mmol); the reagents were dissolved in 0.6 ml of DMSO and the reaction mixture was heated at 150°C overnight. Obtained after flash chromatography 52 mg of the desired compound.

MS (ES/+): 623 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 8.00 (s, 1H), 7.78 (s, 1H), 7.71-7.60 (br. s, 2H), 7.27-7.22 (br. s, 1H), 7.05-6.85 (br. s, 2H), 6.52-6.45 (s, 1H), 4.63-3.98 (m, 2H), 3.74-2.94 (m, 4H), 2.42-2.29 (s, 3H), 2.67-1.86 (m, 3H), 2.17-2.07 (s, 3H), 1.56-1.48 (s, 3H), 1.81-1.12 (m, 4H), 1.41-1.33 (s, 3H).

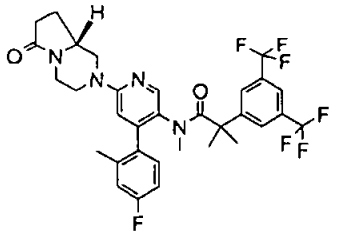
Example 26

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide hydrochloride (E26)



2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E25; 39 mg, 0.063 mmol) was dissolved in DCM and the temperature was lowered at 0°C; HCl (1M soln. in Et_2O) 75µl (0.075mmol) was slowly added and, afterwards, the reaction mixture was stirred at this temperature for 30 min. Then, the solvent was removed and, the solid obtained was triturated with pentane.
Obtained 41 mg of the desired compound as pale yellow solid.
MS (ES/+): 623 $[M+H]^+$
NMR (DMSO-d_6): δ (ppm) 10.63 (s, 1H), 8.02 (s, 1H), 7.96 (s, 1H), 7.81-7.65 (m, 2H), 7.17 (d, 1H), 7.15-7.07 (m, 1H), 6.90- 6.84 (s, 1H), 4.88-4.66 m, 1H), 4.12-1.08 (m, 24H).

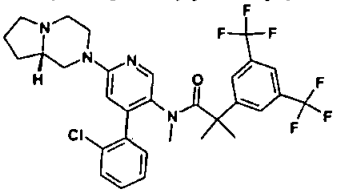
Example 27
2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-6-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E27)



A 8 ml sealed vial was charged with 100 mg (0.187 mmol) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 78.6 mg (0.561 mmol) of (8aS)-hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one (WO 2003/066635), 52 mg (0.374 mmol) of potassium carbonate; the reagents were dissolved in 0.8ml of DMSO. The reaction mixture was heated at 180°C for 36-48hrs and then added to a saturated NH_4Cl solution and back extracted with DCM; the crude material was purified on SPE cartridge (Silica) eluting with a gradient from cyclohexane/ethyl acetate 9:1, to ethyl acetate 100% and affording 23 mg of the desired compound.
MS (ES/+): 637 $[M+H]^+$
NMR (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.05-6.87 (m, 3H); 6.52 (s, 1H); 4.67-4.52 (m, 1H); 4.32-4.19 (m, 1H); 4.14-4.10 (d, 1H); 3.77-3.64 (m, 1H); 3.02-2.84 (m, 2H); 2.61 (t, 1H); 2.48-2.44 (dd, 2H); 2.41-2.33 (s, 3H); 2.30-2.22 (m, 1H); 2.13 (s, 3H); 1.79-1.65 (m, 1H); 1.53 (s, 3H); 1.38 (s, 3H).

Example 28

2-[3,5-Bis(trifluoromethyl)-phenyl]-*N*-{4-(2-chlorophenyl)-6-[(8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E28)



To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-chlorophenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577; 0.11 mmol) in dry DMSO (1 ml) S-octahydropyrrolo[1,2-*a*]pyrazine, (0.22 mmol) and potassium carbonate (0.22 mmol) were added and the resulting mixture was shaken for 12 hours at 150° C. After cooling the dichloromethane was added (2 ml) and then isocyanate polymer bound was added (2.0 mmol), and the resulting mixture was shaken at room temperature overnight. Then the resin was filtered and the filtrate was concentrated under reduced pressure. Purifications were carried out using mass directed HPLC:

Preparative chromatographic conditions

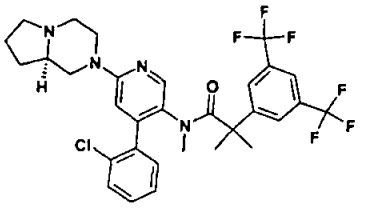
Column: X Terra MS C18 5 µm, 100 x 19 mm
Mobile phase: A: NH_4HCO_3 sol. 10 mM, pH10; B: CH_3CN
Gradient: 30% (B) for 1 min, from 30% (B) to 95% (B) in 9 min, 95% (B) for 3 min
Flow rate: 20 ml/min
UV wavelength range: 210-350 nm
Mass range: 100-900 amu
Ionization: ES+

Analytical chromatographic conditions

Column: X Terra MS C18 5 µm, 50 x 4.6 mm
Mobile phase: A: NH_4HCO_3 sol. 10 mM, pH10; B: CH_3CN
Gradient: 30% (B) for 1 min, from 30% (B) to 95% (B) in 9 min, 95% (B) for 3 min
Flow rate: 1 ml/min
UV wavelength range: 210-350 nm
Mass range: 100-900 amu
Ionization: ES+
Obtained 44.6 mg of the desired compound.
NMR ($CDCl_3$): δ (ppm) 8.03 (s, 1H), 7.90 (s, 1H), 7.74 (s, 2H), 7.54 (2, 2H), 7.49-7.39 (m, 2H), 7.27 (d, 1H), 6.72 (s, 1H), 4.39 (d, 1H), 4.22 (d, 1H), 3.05-2.98 (m, 2H), 2.90-2.83 (t, 1H), 2.57-2.46 (m, 1H), 2.42 (s, 3H), 2.12 (t, 1H), 2.04 (q, 1H), 1.97-1.61 (m, 4H), 1.45-1.19 (m, 7H).

Example 29

2-[3,5-Bis(trifluoromethyl)-phenyl]-*N*-{4-(2-chlorophenyl)-6-[(8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E29)



To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-chlorophenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577; 0.11 mmol) in dry DMSO (1 ml) R-octahydropyrrolo[1,2-*a*]pyrazine, (0.22 mmol) and potassium carbonate (0.22 mmol) were added and the resulting mixture was shaken for 12 hours at 150° C. After cooling the dichloromethane was added (2 ml) and then isocyanate polymer bound was added (2.0 mmol), and the resulting mixture was shaken at room temperature overnight. Then the resin was filtered and the filtrate was concentrated under reduced pressure. Purifications were carried out using mass directed HPLC:

Preparative chromatographic conditions

Column: X Terra MS C18 5 µm, 100 x 19 mm
Mobile phase: A: NH_4HCO_3 sol. 10 mM, pH10; B: CH_3CN
Gradient: 30% (B) for 1 min, from 30% (B) to 95% (B) in 9 min, 95% (B) for 3 min
Flow rate: 20 ml/min
UV wavelength range: 210-350 nm
Mass range: 100-900 amu
Ionization: ES+

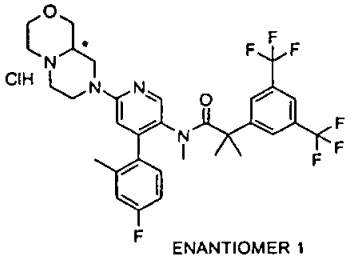
Analytical chromatographic conditions

Column: X Terra MS C18 5 µm, 50 x 4.6 mm
Mobile phase: A: NH_4HCO_3 sol. 10 mM, pH10; B: CH_3CN
Gradient: 30% (B) for 1 min, from 30% (B) to 95% (B) in 9 min, 95% (B) for 3 min
Flow rate: 1 ml/min
UV wavelength range: 210-350 nm
Mass range: 100-900 amu
Ionization: ES+
Obtained 26.3 mg of the desired compound.
NMR (DMSO-d_6): δ (ppm) 8.03 (s, 1H), 7.90 (s, 1H), 7.74 (s, 2H), 7.54 (2, 2H), 7.49-7.39 (m, 2H), 7.27 (d, 1H), 6.72 (s, 1H), 4.39 (d, 1H), 4.22 (d, 1H), 3.05-2.98 (m, 2H), 2.90-2.83 (t, 1H), 2.57-2.46 (m, 1H), 2.42 (s, 3H), 2.12 (t, 1H), 2.04 (q, 1H), 1.97-1.61 (m, 4H), 1.45-1.19 (m, 7H).

150

Example 30

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide hydrochloride (E30) ENANTIOMER 1



ENANTIOMER 1

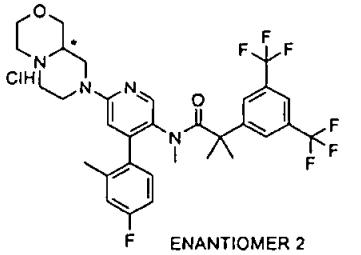
A sample of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E20, 42 mg, 66 µmol) was suspended in 1 ml of anhydrous diethyl ether and treated at 0°C for 30 min with 79 µL of 1M HCl in diethyl ether. The solvent was removed under a stream of nitrogen and the product triturated with anhydrous pentane, to give, after filtration, the hydrochloride as a white solid (44 mg, quantitative).

MS (ES/+): 639 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 10.99 (br. s, 1H), 8.04 (s, 1H), 7.95 9s, 1H), 7.85-7.60 (m, 2H), 7.19 (d, 1H), 7.16-6.92 (m, 2H), 6.92-6.80 (s, 1H), 4.56 (d, 1H), 4.43 (d, 1H), 4.12-3.93 (m, 2H), 3.81 (t, 1H), 3.59 (t, 1H), 3.52-3.45 (m, 1H), 3.29-3.12 (m, 3H), 3.05-2.79 (m, 1H), 2.60-2.52 (m, 1H), 2.33-2.20 (br. s, 3H), 2.22-2.14 (m, 1H), 2.16-2.05 (br. s, 3H), 1.56-1.09 (m, 6H).

Example 31

2-[3,5-Bis(trifluoromethyl)phenyl]-N-[4-(4-fluoro-2-methylphenyl)-6-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-3-pyridinyl]-N,2-dimethylpropanamide hydrochloride (E31) ENANTIOMER 2



ENANTIOMER 2

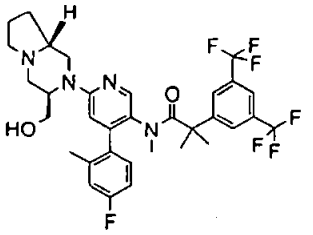
A sample of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E21; 39 mg ,61 µmol) was suspended in 1 ml of anhydrous diethyl ether and treated at 0°C for 30 min with 73 µL of 1M HCl in diethyl ether. The solvent was removed under a stream of nitrogen and the product triturated with anhydrous pentane, to give, after filtration, the hydrochloride as a white solid 41 mg.

MS (ES/+): 639 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 10.99 (br. s, 1H), 8.04 (s, 1H), 7.95 9s, 1H), 7.85-7.60 (m, 2H), 7.19 (d, 1H), 7.16-6.92 (m, 2H), 6.92-6.80 (s, 1H), 4.56 (d, 1H), 4.43 (d, 1H), 4.12-3.93 (m, 2H), 3.81 (t, 1H), 3.59 (t, 1H), 3.52-3.45 (m, 1H), 3.29-3.12 (m, 3H), 3.05-2.79 (m, 1H), 2.60-2.52 (m, 1H), 2.33-2.20 (br. s, 3H), 2.22-2.14 (m, 1H), 2.16-2.05 (br. s, 3H), 1.56-1.09 (m, 6H).

Example 32

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*R*,8a*R*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E32)



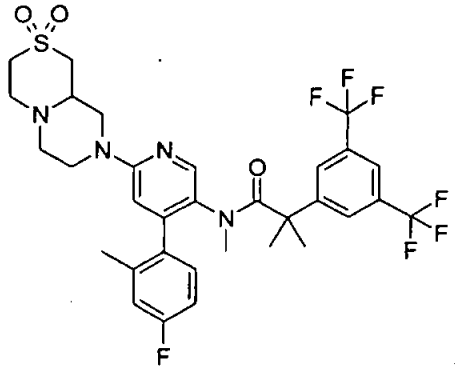
The title compound was prepared starting from 323 mg (0.608 mmoles) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577), 1.216 mg (0.160 mmol) of (3*R*,9a*R*)-octahydro-2H-pyrido[1,2-a]pyrazin-3-ylmethanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005), 35mg of bis(dibenzylideneacetone)palladium (0.061 mmol), 57 mg of 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (0.145 mmol), 297 mg (0.912 mmol) of cesium carbonate; the reagents were dissolved in 10ml of toluene and stirred at 140°C in a closed vial for 4 hours. More dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (57 mg 0.145 mmol), and bis(dibenzylideneacetone)palladium (35 mg, 0.061 mmol) were added and the reaction kept at 140°C for additional 4 hours. The crude material was loaded on a SCX cartridge, the neutral fractions were washed with methanol and the basic eluted with 2M ammonia in methanol and collected. The solvent was removed and the residue purified by chromatography (Silica) eluting with ethyl acetate, followed by a gradient from methylene chloride to methylene chloride:methanol 95:5. The cleanest fractions were purified further by chromatography on an NH_2 silica cartridge with a gradient cyclohexane to cyclohexane:ethyl acetate 70:30, affording 29 mg of the title compound as pale yellow solid.

MS (ES/+): 653 $[M+H]^+$

NMR (DMSO-d_6): δ (ppm) 7.89-7.86 (s, 1H); 7.80-7.76 (s, 1H); 7.70-7.66 (s, 2H); 7.12-7.03 (m, 2H); 7.00-6.92 (m, 1H); 6.50-6.47 (s,1H); 4.06-3.97 (m, 1H); 3.66-3.54 (m, 3H); 3.49-3.39 (m, 1H); 3.27-3.12 (m, 1H); 3.11-3.00 (m, 1H); 2.89-2.77 (m, 2H); 2.44-2.38 (s, 3H); 2.17-2.07 (s, 3H); 2.07-1.41 (m, 5H); 1.38-1.31 (s, 3H); 1.26-1.20 (s, 3H).

Example 33

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-(2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E33)

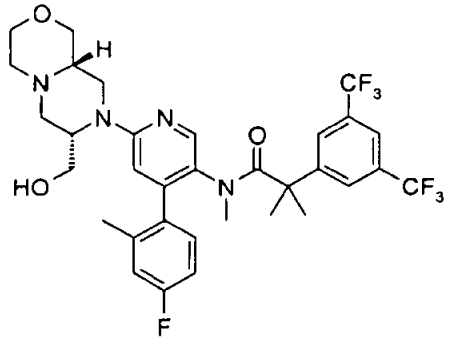


A 8 ml sealed vial was charged with 180 mg (0.31 mmol) of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (WO 2005/002577); 168 mg (0.62 mmol) of octahydropyrazino[2,1-*c*][1,4]thiazine 2,2-dioxide (D19), 128 mg (0.701 mmol) of potassium carbonate; the reagents were dissolved in 1 ml of DMSO and stirred at 150°C for 18h. The reaction mixture was diluted with water and ethyl acetate and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were dried and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica, cyclohexane/EtOAc 50/50 to EtOAc) affording the title compound as a white solid 105 mg. MS (ES/+): $[M+Na]^+$.

NMR (DMSO-d_6): δ (ppm) 8.07-7.99 (s, 1H), 7.97-7.86 (s, 1H), 7.82-7.62 (m, 2H), 7.22-7.12 (d, 1H), 7.15-6.98 (m, 2H), 6.79-6.69 (s, 1H), 4.32-4.13 (m, 2H), 3.31-3.07 (m, 5H), 3.04-2.84 (m, 3H), 2.73-2.55 (m, 2H), 2.57-2.43 (m, 3H), 2.36-2.18 (m, 1H), 2.29-2.05 (m, 3H); 1.60-1.27 (m, 6H).

Example 34

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E34)



inhibitors (such as atomoxetine), alpha 2 adrenoceptor agonists (such as clonidine), antidepressants, modafinil, and cholinesterase inhibitors (such as galantamine and donezepil).

The compounds of the invention may be used in combination with the following agents to treat personality disorders: i) antipsychotics; ii) antidepressants; iii) mood stabilisers; and iv) anxiolytics.

The compounds of the invention may be used in combination with the following agents to treat or prevent male sexual dysfunction: i) phosphodiesterase V inhibitors, for example vardenafil and sildenafil; ii) dopamine agonists/dopamine transport inhibitors for example apomorphine and buproprion; iii) alpha adrenoceptor antagonists for example phentolamine; iv) prostaglandin agonists for example alprostadil; v) testosterone agonists such as testosterone; vi) serotonin transport inhibitors for example serotonin reuptake inhibitors; v) noradrenaline transport inhibitors for example reboxetine and vii) 5-HT1A agonists, for example flibanserine.

The compounds of the invention may be used in combination with the same agents specified for male sexual dysfunction to treat or prevent female sexual dysfunction, and in addition an estrogen agonist such as estradiol.

Antipsychotic drugs include Typical Antipsychotics (for example chlorpromazine, thioridazine, mesoridazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thiothixine, haloperidol, molindone and loxapine); and Atypical Antipsychotics (for example clozapine, olanzapine, risperidone, quetiapine, aripirazole, ziprasidone and amisulpride).

Antidepressant drugs include serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, paroxetine and sertraline); dual serotonin/noradrenaline reuptake inhibitors (such as venlafaxine, duloxetine and milnacipran); Noradrenaline reuptake inhibitors (such as reboxetine); tricyclic antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline and trimipramine); monoamine oxidase inhibitors (such as isocarboxazide, moclobemide, phenelzine and tranylcypromine); and others (such as bupropion, mianserin, mirtazapine, nefazodone and trazodone).

Mood stabiliser drugs include lithium, sodium valproate/valproic acid/divalproex, carbamazepine, lamotrigine, gabapentin, topiramate and tiagabine.

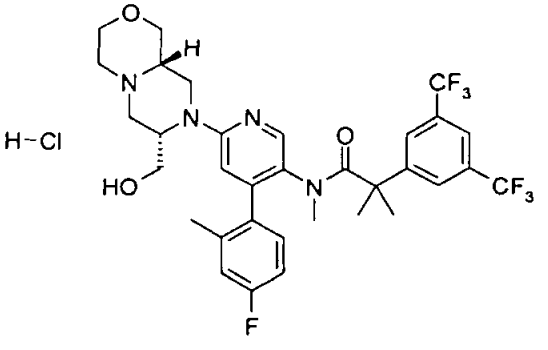
Anxiolytics include benzodiazepines such as alprazolam and lorazepam.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D24) (390 mg, 0.498 mmol) was dissolved 17 mL of methanol. To this solution was added concentrated HCl (0.9 mL) at 0°C, and stirring was continued at room temperature for 3h (complete conversion). The reaction mixture was loaded on a SCX cartridge and washed with MeOH. The product was eluted with 0.5 M methanolic ammonia. The product-containing fractions were evaporated, leaving the target compound as a white solid: 310 mg, 0.464 mmol, 93%.
UPLC/MS: m/z= 669 (M+1).
^{1}H-NMR (DMSO-d_6): δ (ppm) 8.07-7.97 (s, 1H), 7.88-7.81 (s, 1H), 7.79-7.69 (br. s, 2H), 7.19-7.11 (d, 1H), 7.14-7.06 (br. s, 2H) 6.64-6.56 (s, 1H), 4.75-4.65 (m, 1H), 4.31-4.13 (br. S, 1H), 4.15-4.01 (br. s, 1H), 3.80-3.68 (m, 3H), 3.58-3.49 (t, 1H); 3.43-3.34 (m, 1H); 3.18-3.09 (t, 1H); 3.04-2.98 (d, 1H); 2.68-2.58 (d, 1H); 2.51-2.45 (s, 3H); 2.20-2.13 (s, 3H); 2.29-2.00 (m, 4H); 1.54-1.39 (s, 3H); 1.39-1.28 (s, 3H).

Example 35

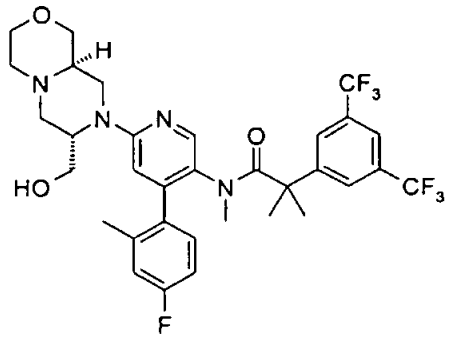
2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide Hydrochloride (E35)



To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E34) (300 mg, 0.449 mmol) in 2 mL of diethyl ether was added 0.6 mL of a 1M HCl solution in diethyl ether. A white precipitate formed. The solvent and excess HCl were removed under a stream of nitrogen and the residue was triturated with 1 mL of 1:1 pentane: Et_2O. The white solid was collected by filtration and left under high vacuum to give the title compound 280 mg, 0.397 mmol, 88% yield.
1H NMR (500 MHz, DMSO-d_6) δ ppm 10.24 (br. s., 1 H) 8.03 (br. s., 1 H) 7.90 (br. s., 1 H) 7.55 - 7.82 (m, 2 H) 6.89 - 7.24 (m, 3 H) 6.77 (br. s., 1 H) 4.65 (br. s., 1 H) 4.45 (br. s., 1 H) 3.92 - 4.15 (m, 2 H) 3.76 - 3.90 (m, 2 H) 3.34 - 3.55 (m, 2 H) 3.09 - 3.36 (m, 2 H) 2.84 - 3.04 (m, 1 H) 2.49 - 2.62 (m, 2 H) 2.01 - 2.30 (m, 6 H) 1.10 - 1.58 (m, 8 H).
α_D (c = 0.5 in MeOH) = -39.6 obtained using a polAAR 3000 polarimeter, λ = 589.4nm, cell volume = 1.3ml, path length, l = 1dm. (This value was determined on a different sample, spectroscopically the same as that described above and prepared in an analogous way).

Example 36

2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E36)



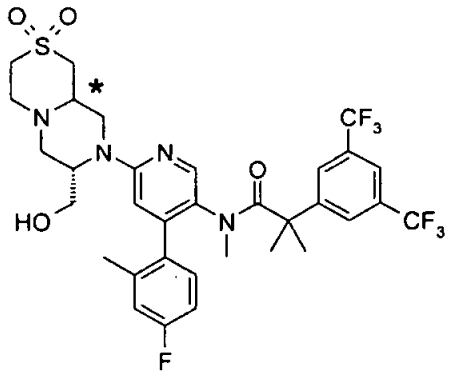
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*S*,9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D25) (87 mg, 0.111 mmol) was dissolved 4 mL of methanol. To this solution was added concentrated HCl (0.2 mL) at 0°C, and stirred at room temperature for 1h (complete conversion). The reaction mixture was loaded on a SCX cartridge and washed with MeOH. The product was eluted with 0.5 M methanolic ammonia. The UV-active basic fractions were evaporated, leaving the target compound as a white solid: 69 mg, 0.103 mmol, 93%.

MS: m/z= 669 (M+1).

^{1}H-NMR (DMSO-d_6): δ (ppm) 8.07-7.97 (m, 1H), 7.95-7.89 (br. s, 1H), 7.81-7.67 (br. s, 2H), 7.20-7.10 (d, 1H), 7.16-7.04 (br. s, 2H), 6.75-6.65 (br. s, 1H), 4.87-4.78 (br. s, 1H), 3.96-3.79 (br. s, 1H), 3.66-3.47 (m, 4H), 3.42-3.34 (m, 1H), 3.32-3.23 (m, 1H); 3.17-3.07 (dd, 1H); 2.71-2.63 (dd, 1H); 2.61-2.39 (m, 2H); 2.50-2.44 (s, 3H); 2.39-1.99 (m, 3H); 2.16-2.02 (br. s, 3H); 1.58-1.42 (s, 3H); 1.40-1.27 (s, 3H).

Example 37

2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*, 9a*R* or 9a*S*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide (E37)-Diastereoisomer 1



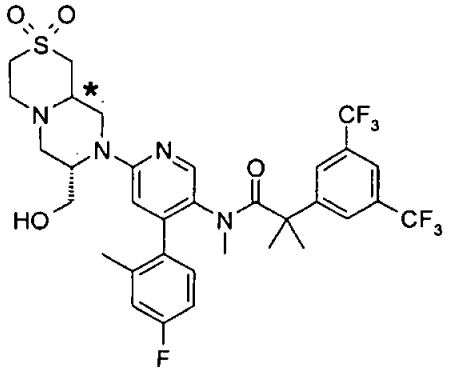
To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-N-[6-[(7*S*, 9a*R* or 9a*S*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D31) (170 mg, 0.2 mmol) in 8 mL of methanol was added dropwise HCl 12 N (0.4 mL) at 0°C. The reaction mixture was stirred at room temperature for 1.5 hrs, then it was purified by SCX cartridge to give the title compound as a white solid (120 mg, yield=81%).

HPLC : peak @ t=5.54 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.85 (s, 1 H) 7.63 - 7.81 (m, 2 H) 7.16 (d, 1 H) 7.03 - 7.17 (m, 2 H) 6.67 (s, 1 H) 4.71 (t, 1 H) 4.19 - 4.36 (m, 1 H) 4.02 - 4.19 (m, 1 H) 3.65 - 3.80 (m, 1 H) 3.36 - 3.53 (m, 1 H) 3.24 - 3.36 (m, 2 H) 3.15 - 3.29 (m, 2 H) 3.10 (d, 1 H) 2.86 - 3.01 (m, 1 H) 2.72 - 2.84 (m, 1 H) 2.65 (d, 1 H) 2.49 (s, 3 H) 2.42 - 2.56 (m, 2 H) 2.20 (s, 3 H) 1.49 (s, 3 H) 1.34 (s, 3 H).

Example 38

2-[3,5-Bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*, 9a*S* or *R*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide (E38)-Diastereomer 2



2-[3,5-Bis(trifluoromethyl)phenyl]-N-[6-[(7*S*, 9a*S* or *R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-N,2-dimethylpropanamide (D36) (158 mg, 0.190 mmol) was dissolved 10 mL of methanol. To this solution was added dropwise

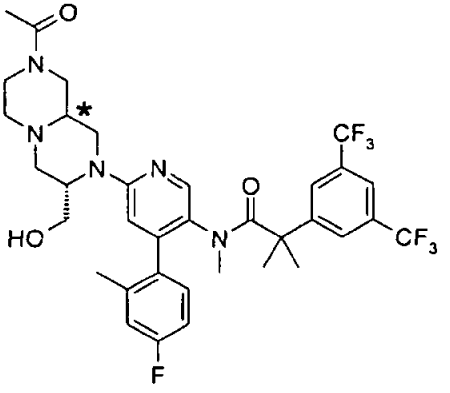
concentrated HCl (0.4 mL) at 0°C, and stirred at room temperature for 1.5 h (complete conversion by UPLC/MS, peak at 0.87 min., m/z = 717 (M+1), 359 ($^{M}/_{2}$ +1). The reaction mixture was purified by SCX cartridge, leaving the target compound as a solid: 107 mg, 0.149 mmol, 78%.

MS: m/z= 669 (M+1).

1H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 - 8.07 (m, 1 H) 7.81 - 7.93 (m, 1 H) 7.62 - 7.81 (m, 2 H) 6.90 - 7.24 (m, 3 H) 6.57 - 6.71 (m, 1 H) 4.65 - 4.76 (m, 1 H) 4.09 - 4.38 (m, 1 H) 3.65 - 3.79 (m, 1 H) 3.30 - 3.49 (m, 2 H) 3.05 - 3.28 (m, 5 H) 3.00 (t, 1 H) 2.65 - 2.79 (m, 1 H) 2.37 - 2.50 (m, 1 H) 2.01 - 2.33 (m, 7 H) 1.10 - 1.55 (m, 6 H).

Example 39

***N*-[6-[(3*S*, 9a*R* or *S*)-8-acetyl-3-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E39)-Diastereoisomer 1**

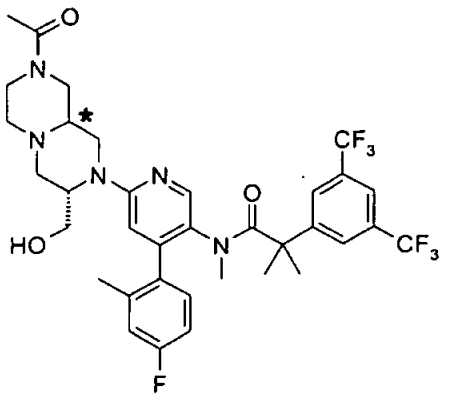


N-[6-[(3*S*, 9a*R* or *S*)-8-acetyl-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D41) (1.168 g, 1.42 mmol) was dissolved in 40 mL of methanol. To this solution was added concentrated HCl (2.5 mL) at 0°C, and stirred at room temperature for 1 h. UPLC/MS analysis showed complete conversion to the expected product (peak at 0.75 min, m/z = 710 (M+1), 355.7 ($^{M}/_{2}$ +1)). The reaction mixture was purified by SCX cartridge, followed by flash chromatography (CH_2Cl_2 -> CH_2Cl_2 : MeOH 92.5 : 7.5), to give target compound as a solid: 483 mg, - mmol, 78%.

1H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 - 8.06 (m, 1 H) 7.80 - 7.89 (m, 1 H) 7.60 - 7.80 (m, 2 H) 6.90 - 7.24 (m, 3 H) 6.54 - 6.76 (m, 1 H) 4.66 - 4.74 (m, 1 H) 4.04 - 4.43 (m, 2 H) 3.67 - 3.91 (m, 2 H) 3.32 - 3.47 (m, 1 H) 3.13 - 3.23 (m, 1 H) 3.00 - 3.10 (m, 1 H) 2.68 - 2.87 (m, 2 H) 2.55 - 2.69 (m, 2 H) 1.78 - 2.40 (m, 12 H) 1.11 - 1.58 (m, 6 H)

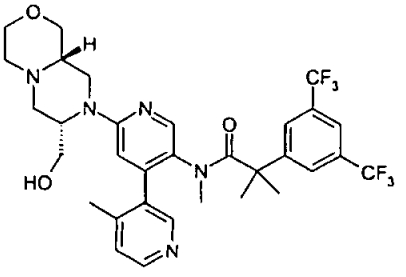
Example 40

***N*-[6-[(3*S*, 9a*S* or *R*)-8-acetyl-3-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E40)-Diastereoisomer 2**



N-[6-[(3*S*, 9a*S* or *R*)-8-acetyl-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D42) was treated as described for *N*-[6-[(3*S*, 9a*R* or *S*)-8-acetyl-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D41) above. UPLC/MS analysis showed complete conversion to the expected product (peak at 0.71 min, m/z = 710 (M+1), 355.7 ($^{M}/_{2}$ +1)).The product was purified in the same way, yielding 700 mg.
1H NMR (500 MHz, DMSO-d_6) δ ppm 7.97 - 8.06 (m, 1 H) 7.86 - 7.94 (m, 1 H) 7.61 - 7.82 (m, 2 H) 6.92 - 7.21 (m, 3 H) 6.64 - 6.79 (m, 1 H) 4.75 - 4.84 (m, 1 H) 4.05 - 4.17 (m, 1 H) 3.90 - 4.05 (m, 1 H) 3.45 - 3.69 (m, 4 H) 3.33 - 3.45 (m, 1 H) 3.18 - 3.30 (m, 1 H) 3.05 - 3.18 (m, 2 H) 2.69 - 2.83 (m, 1 H) 2.51 - 2.64 (m, 2 H) 2.32 - 2.45 (m, 2 H) 2.05 - 2.29 (m, 5 H) 1.93 - 2.01 (m, 3 H) 1.09 - 1.56 (m, 6 H).

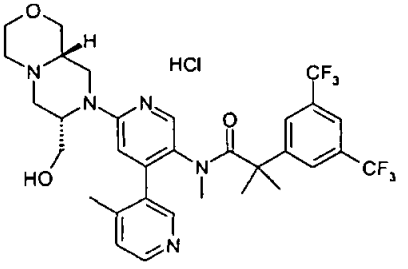
Example 41: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6'-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-methyl-3,4'-bipyridin-3'-yl}-*N*,2-dimethylpropanamide (E41)



2-[3,5-bis(trifluoromethyl)phenyl]-N-{6'-[(7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-4-methyl-3,4'-bipyridin-3'-yl}-N,2-dimethylpropanamide (D53, 86mg) was dissolved in dry MeOH (4mL), cooled in an ice/salt bath to ~0°C before adding c.HCl solution. The mixture was stirred at ~0°C for 45mins before allowing to warm

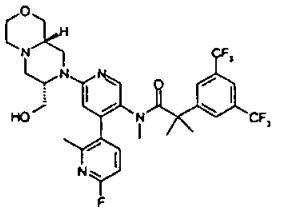
up to R.T. and stirring for a further 2hrs. Placed on a 5g SCX column, washed with MeOH x3, before eluting compound off with NH3 in MeOH. Solvent evaporated. Residue purified on a 5g sek pak column eluting with Pent to EtOAc to 10%MeOH/EtOAc. Solvent evaporated to dryness in vacuo to afford a colourless gum of the title compound.
NMR (DMSO- d6) δ 8.44 (1H, d), 8.21 (1H, s), 8.04 (1H, s), 7.89 (1H, s), 7.73 (2H, s), 7.33 (1H, d), 6. 70 (1H, s), 4.71 (1H, br t), 4.23 (1H, br s), 4.10 (1h, br s), 3.76 (3H,m), 3.55 (1H, t), 3.41 (2H, m), 3.16 (1H, t), 3.02 (1H, d), 2.66 (1H, m), 2.33-2.05 (7H, m), 1.47- 1.17 (6H, br m)
MS (API+): m/z 652.1 (MH+; 20%).

Example 42: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6'-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-methyl-3,4'-bipyridin-3'-yl}-*N*,2-dimethylpropanamide hydrochloride (E42)



Title compound was made by dissolving 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6'-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-methyl-3,4'-bipyridin-3'-yl}-*N*,2-dimethylpropanamide (E41, 33.8mg) in minimum of DCM, adding 1M HCl solution in Et2O, adding Et2O, triturating till a solid precipitates out. Liquors removed. More Et2O added triturated again. Solvent blown dry to afford a white solid.
MS (API+): m/z = 652.3 (MH+; 20%)

Example 43: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6-fluoro-6'-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-2-methyl-3,4'-bipyridin-3'-yl}-*N*,2-dimethylpropanamide (E43)



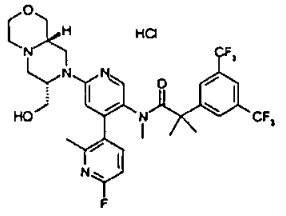
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2-[3,5-bis(trifluoromethyl)phenyl]-N-(6'-chloro-6-fluoro-2-methyl-3,4'-bipyridin-3'-yl)-N,2-dimethylpropanamide (D54, 53.5mg, 0.1mmol), (7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-c][1,4]oxazine (D51, 37mg, 0.13mmol) were dissolved in toluene (1.5mL). Bis tritertbutylphosphine palladium (13mg, 0.026mmol), followed by hexadecyltrimethylammoium chloride (10μL, 25% aq sol), and finally sodium hydroxide solution (0.13mL, 50% aq sol). The mixture was degassed for 5 minutes before heating at 90°C for 4.5 hours. Cooled to R.T., diluted with EtOAc, washed with sat. $NaHCO_3$ solution, dried ($MgSO_4$). Filtered. Solvent evaporated. Residue purified by SCX column, washing with MeOH before eluting with NH_3 in MeOH. Solvent evaporated. Residue purified by column chromatography eluting with Pent to EtOAc to 10% MeOH/EtOAc. Solvent evaporated under reduced pressure to afford a colourless solid of the title compound (11mg).

NMR (400MHz, CDCl3) δ 7.98 (1H, s), 7.79 (1H, s), 7.73-7.70 (1H, br m), 7.64 (1H, s), 6.82 (1H, s), 6.43 (1H, s), 4.55 (1H,d), 4.02 (2H, s), 3.90 (1H, d), 3.81 (2H, t), 3.67 (1H, m), 3.33 (1H, t), 3.12- 3.06 (2H,m), 2.77 (1H, d), 2.54 – 2.30 (10H, m), 1.49 (3H,s), 1.35 (3H,s)

MS (API+): m/z 670.3 (MH+; 100%)

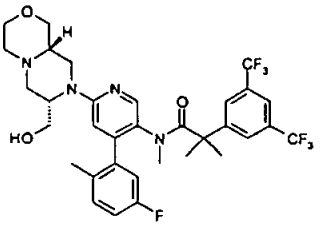
Example 44: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6-fluoro-6'-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-2-methyl-3,4'-bipyridin-3'-yl}-*N*,2-dimethylpropanamide hydrochloride (E44)



HCl salt made as described in example 41 starting from 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6-fluoro-6'-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-2-methyl-3,4'-bipyridin-3'-yl}-*N*,2-dimethylpropanamide (E43, 11.3mg)to afford an off white solid.

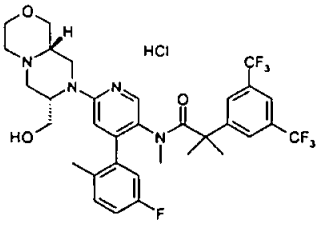
MS (API+): m/z 670.3 (MH+; 100%)

Example 45: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(5-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E45)



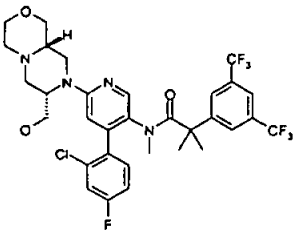
2-[3,5-bis(trifluoromethyl)phenyl]-N-[6-[(7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-4-(5-fluoro-2-methylphenyl)-3-pyridinyl]-N,2-dimethylpropanamide (D56, 110mg) was dissolved in dry MeOH (2mL), cooled in an ice-salt bath before adding cHCl solution (~0.2mL), and stirring at R.T. for 2 hours. Poured directly onto a 5g SCX column. Washed with MeOH (2 x10mL), before eluting the compound with NH_3 in MeOH 94 x10mL). Solvent evaporated. Residue purified on a 5g sek-pak column eluting with Pent to EtOAc to 10%MeOH/EtOAc. Solvent evaporated to afford the title compound as a white solid.
NMR (400MHz ; CDCl3) δ 7.98 (1H, br s), 7.77 (1H, s), 7.67 (2H, s), 7.21 (1H, br s), 7.00 (2H, m), 6.44 (1H, s), 4.57 (1H, br s), 4.20- 4.08 (1H, br m), 4.02 (2H, s), 3.89 (1H, dd), 3.81 (2H, d), 3.70 (1H, m), 3.33 (1H, t), 3.11- 3.05 (2H, m), 2.76 (1H, d), 3.63 (1H, d), 2.42- 2.30 (4H, m), 2.29- 2.05 (4H, m), 1.51- 1.32 (6H, m)
MS (API+): m/z 669.3 (MH+; 100%)

Example 46: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(5-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide hydrochloride (E46)



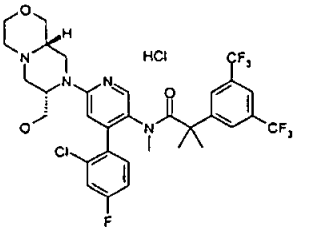
HCl salt made according to method described in Example 41 starting from 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(5-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E45, 11.5mg) to afford a pale yellow solid
MS (API+): m/z 669.3 (MH+; 100%)

Example 47: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(2-chloro-4-fluorophenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E47)



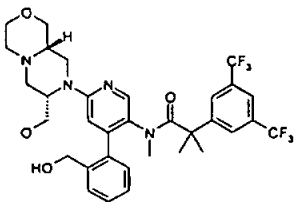
2-[3,5-bis(trifluoromethyl)phenyl]-N-{4-(2-chloro-4-fluorophenyl)-6-[(7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-3-pyridinyl}-N,2-dimethylpropanamide (D58, 22mg, 0.027mmol) was dissolved in dry MeOH (2mL), cooled in an ice-salt bath to ~0°C before adding c.HCl solution (~ 0.1mL), slowly. The reaction mixture was stirred at ~0°C for 1 hour before warming up and stirring at R.T. for 2 hours. Placed directly onto a 2g SCX column, washing with MeOH (2 x 5mL) before eluting the compound off with NH_3 in MeOH (4 x 5mL). Solvent evaporated under reduced pressure to afford the title compound as an off white solid. (10mg)
NMR (400MHz, DMSO-d6) δ 8.03 (1H,s), 7.89 (1H, s), 7.71 (2H, s), 7.55 (1H, d), 7.34 (2H, m), 6.65 (1H,s), 4.71 (1H,t), 4.22 (1H, br m), 4.07 (1H, br m), 3.76 (2H,m), 3.55 (1H, t), 3.15 (1H,t), 3.03 (1H, m), 2.68- 2.60 (2H,m), 2.50- 2.40 (3H, m), 2.18- 2.05 (3H, m), 1.45 (3H,s), 1.31 (3H,s)
MS (API+): m/z 689.3 (MH+; 100%)

Example 48: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(2-chloro-4-fluorophenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide hydrochloride (E48)



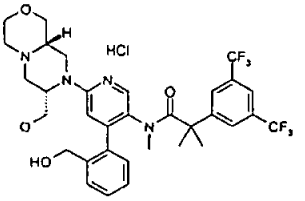
HCl salt made according to method described in Example 41 starting from 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(2-chloro-4-fluorophenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E47, 10mg) to afford a pale yellow solid.
MS (API+): m/z 689.2 (MH+; 100%)

Example 49: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-[2-(hydroxymethyl)phenyl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E49)



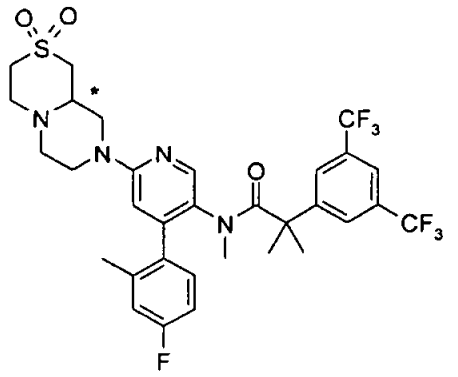
2-[3,5-bis(trifluoromethyl)phenyl]-N-{6-[(7S,9aS)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]-4-[2-(hydroxymethyl)phenyl]-3-pyridinyl}-N,2-dimethylpropanamide (D61, 24.6mg, 0.0315mmol) was suspended in dry MeOH (1mL) before adding c.HCl solution (5 drops). The reaction mixture was then stirred at R.T. for 3 hours. Poured directly onto a 5g SCX column, washing with MeOH (2 x 10mL) before eluting the compound off with NH_3 in MeOH (4 x 10mL). Solvent evaporated. Residue purified on a 5g sek pak column eluting with 0 – 100% EtOAc/Pent followed by 0 -10% MeOH/EtOAc. Solvent evaporated to afford the title compound as a colourless gum.
NMR (400MHz, CDCl3) δ 7.94 (1H, d), 7.78 (1H, s) , 7.66- 7.59 (3H, m), 7.43 (1H, t), 7.28 (1H, m), 7.00- 6.96 (1H, m), 6.46 (1H, d), 4.67 (1H, m), 4.53 (1H,d), 4.42- 4.34 (1H, m), 4.05 – 3.98 (2H, m), 3.90- 3.67 (6H,m), 3.35- 3.30 (1H,m), 3.09- 3.00 (2H,m), 2.72 (3H,d), 2.63 (1H,dd), 2.45- 2.30 (3H,m), 1.30 (6H,s)
MS (API+): m/z 667. 3(MH+; 100%)

Example 50: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-[2-(hydroxymethyl)phenyl]-3-pyridinyl}-*N*,2-dimethylpropanamide hydrochloride (E50)



HCl salt made according to method described in Example 41 starting from 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-[2-(hydroxymethyl)phenyl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E49, 10.2mg) to afford a yellow solid.
MS (API+): 667.3 (MH+; 100%)

Example 51: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(9a*R* *or* *9aS*)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E51- Enantiomer 1)



N-[6-(8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E33, 101 mg) was submitted for chiral separation to isolate its enantiomers. The Enantiomer labeled **1**, of unknown but single stereochemistry was isolated using preparative conditions described below (obtained 12 mg of title compound, >95%e.e., analytical retention time 10.23 min).

Semipreparative SFC (Gilson) conditions:

Amount supplied	101 mg
Chiral Column	CHIRALCEL OD-H, (25 x 2) cm
Mobile phase	n-Hexane/2-propanol 94/6 % v/v
Flow rate	18 ml/min
Detection	UV at 225 nm

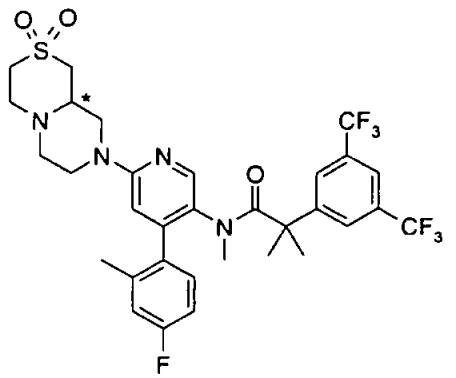
Analytical SFC (Berger) conditions:

Chiral Column	CHIRALCEL OD-H, (25 x 0.46) cm
Mobile phase	n-Hexane/ethanol 70/30 % v/v
Flow rate	0.8 ml/min
Detection	UV at 225 nm

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (br. s., 1 H) 7.89 (br. s., 1 H) 7.61 - 7.84 (m, 2 H) 7.16 (d, 1 H) 6.90 - 7.14 (m, 2 H) 6.72 (br. s., 1 H) 4.12 - 4.31 (m, 2 H) 3.08 - 3.32 (m, 5 H) 2.85 - 3.03 (m, 3 H) 2.52 - 2.73 (m, 2 H) 2.01 - 2.32 (m, 7 H) 1.13 - 1.59 (*m*, 6 H)

MS (direct): 687 (M+1)

Example 52: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(9a*S* *or* 9a*R*)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E52 - Enantiomer 2)

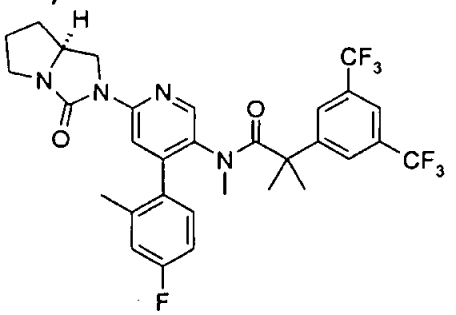


The title compound was obtained as the second compound, labeled Enantiomer 2, from the chiral separation performed on 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*-[6-(2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E33) as reported for 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(9a*R or 9aS*)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E51)(obtained 70 mg, >95.5%e.e., analytical retention time 14.56 min).

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (br. s., 1 H) 7.89 (br. s., 1 H) 7.61 - 7.84 (m, 2 H) 7.16 (d, 1 H) 6.90 - 7.14 (m, 2 H) 6.72 (br. s., 1 H) 4.12 - 4.31 (m, 2 H) 3.08 - 3.32 (m, 5 H) 2.85 - 3.03 (m, 3 H) 2.52 - 2.73 (m, 2 H) 2.01 - 2.32 (m, 7 H) 1.13 - 1.59 (m, 6 H)

MS (direct): 687 (M+1)

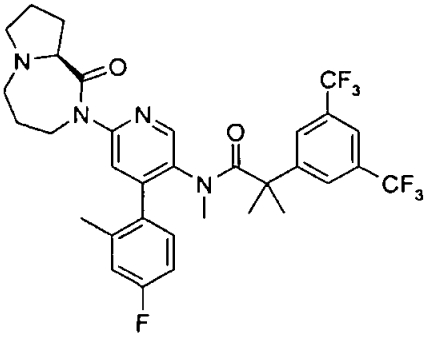
Example 53: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7a*S*)-3-oxotetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-2(3*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E53)



The starting 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-(4-(4-fluoro-2-methylphenyl)-6-{[(2*S*)-2-pyrrolidinylmethyl]amino}-3-pyridinyl)-*N*,2-dimethylpropanamide (D62, 38 mg, 0.064 mmol) was dissolved in 1 mL of anhydrous dichloromethane and treated with triethylamine (20 µL, 0.143 mmol). The solution was brought to 0°C and triphosgene (10 mg, 0.034 mmol) was added. The reaction was stirred at 0°C for 15 min, then brought to room temperature. After 24 h, the reaction was diluted with dichloromethane (10 mL) and extracted with brine. The organics were collected and

the solvent removed. The product was isolated by flash chromatography (silica, cyclohexane: EtOAc 80:20 to EtOAc). Thus were obtained 8 mg of the target compound.
HPLC/MS: m/z= 623 (M+1),
1H NMR (400 MHz, DMSO-d_6) δ ppm 8.03 (s, 1 H) 8.00 (s, 1 H) 7.89 (s, 1 H) 7.66 - 7.72 (m, 2 H) 7.04 - 7.13 (m, 2 H) 6.94 - 7.04 (m, 1 H) 4.10 (t, 1 H) 3.94 (dd, 1 H) 3.74 - 3.84 (m, 1 H) 3.47 - 3.59 (m, 1 H) 2.90 - 3.08 (m, 1 H) 2.43 (s, 3 H) 2.09 (s, 3 H) 1.97 - 2.10 (m, 1 H) 1.74 - 1.98 (m, 2 H) 1.47 - 1.73 (m, 1 H) 1.36 (s, 6 H)

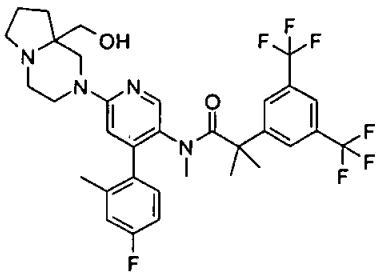
Example 54: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*S*)-1-oxohexahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-2(3*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E54)



A solution of (9a*S*)-octahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one (Polish Journal of Chemistry, 59(10-12), 1243-6; 1985) (31 mg, 0.201 mmol), 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (53 mg, 0.0996 mmol), N,N'-dimethyethylendiamine (22µL, 0.207 mmol), copper(I) iodide (38 mg, 0.200 mmol) and caesium carbonate (65 mg, 0.199 mmol) in 3 mL of dioxane was heated to 100°C in a sealed vial overnight. Heating was continued for additional 2 days. It was diluted with 10 mL of EtOAc and extracted with water. The organics were dried (Na_2SO_4) and the solvent removed. The product was isolated by flash chromatography (silica, cyclohexane: EtOAc 90:10 to 30: 70). Thus were obtained 14 mg of the target compound.
HPLC/MS: m/z= 651 (M+1), >99% by UV.
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.34 (s, 1 H) 8.10 (s, 1 H) 7.84 (br. s., 2 H) 7.77 (br. s., 1 H) 7.57 (s, 1 H) 7.25 (d, 1 H) 7.19 (br. s., 1 H) 4.54 (br. s., 1 H) 3.96 (t, 1 H) 3.72 (dd, 1 H) 3.25 (dd, 1 H) 3.02 - 3.09 (m, 1 H) 2.53 - 2.67 (m, 1 H) 2.43 (s, 3 H) 2.28 - 2.42 (m, 1 H) 2.19 (s, 3 H) 1.81 - 1.91 (m, 1 H) 1.66 - 1.78 (m, 2 H) 1.60 (s, 3 H) 1.44 (s, 3 H) 1.26 - 1.38 (m, 1 H) 1.11 - 1.22 (m, 1 H) 0.89 - 1.07 (m, 1 H)

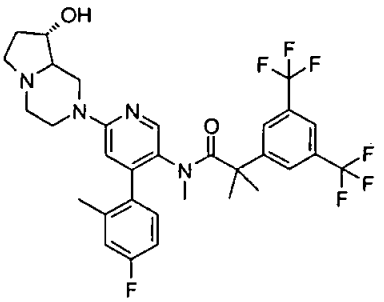
Example 55: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-

[8a-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E55)



To a solution of hexahydropyrrolo[1,2-*a*]pyrazin-8a(6*H*)-ylmethanol (D67, 35 mg) in methyl sulfoxide (1.5 mL), 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (60 mg) and potassium carbonate (63 mg) were added. The resulting mixture was heated at 150°C for 24 hours. The mixture was allowed to cool down to r.t and further D67 (17 mg) and potassium carbonate (15 mg) were added. The resulting mixture was heated at 150°C for further 8 hours and then it was allowed to cool to r.t. and diluted with water (2 mL). The aqueous phase was extracted with ethyl acetate (3 x 2.5 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified twice by flash chromatography (first purification: EtOAc/Cycl from 80/20 to 100:0 then DCM/MeOH 95:5. Second purification: DCM/MeOH 98:2) to give the desired compound (7.7 mg) as yellow foam.
T.l.c.: DCM/MeOH 9:1, Rf=0.29.
UPLC/MS: peak at Rt = 0.673 min with m/z = 653 $[M+H]^+$.
1H NMR (300 MHz, DMSO-d_6) δ ppm 7.94 (s, 1 H) 7.82 (br. s., 1 H) 7.73 (s, 2 H) 7.07 - 7.20 (m, 2 H) 6.96 - 7.07 (m, 1 H) 6.46 (s, 1 H) 3.90 (d, 1 H) 3.37 - 3.60 (m, 3 H) 3.11 - 3.32 (m, 4 H) 2.80 - 2.95 (m, 2 H) 2.47 (s, 3 H) 2.18 (s, 3 H) 1.61 - 1.82 (m, 2 H) 1.40 (s, 6 H) 1.32 - 1.54 (m, 2 H).

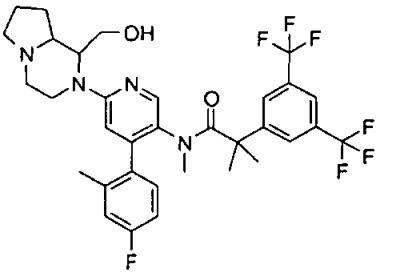
Example 56: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8*S*)-8-hydroxyhexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E56)



To a solution of (8*S*)-octahydropyrrolo[1,2-*a*]pyrazin-8-ol (D71, 32 mg) in methyl sulfoxide (1.2 mL), 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-

methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (60 mg) and potassium carbonate (63 mg) were added. The resulting mixture was heated at 150°C for 24 hours. The mixture was allowed to cool down to r.t. and diluted with water (2 mL). The aqueous phase was extracted with ethyl acetate (3 x 2.5 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (DCM/MeOH from 100:0 to 95:5) to give the desired compound (18.8 mg) as yellow foam.
T.l.c.: DCM/MeOH 9:1, Rf=0.48.
UPLC/MS: peak at Rt = 0.71 min with m/z = 639 $[M+H]^+$.
1H NMR (300 MHz, DMSO-d_6) δ ppm 7.95 (s, 1 H) 7.86 (br. s., 1 H) 7.74 (s, 2 H) 7.07 - 7.20 (m, 2 H) 6.98 - 7.08 (m, 1 H) 6.59 (s, 1 H) 4.12 - 4.35 (m, 3 H) 2.82 - 2.99 (m, 3 H) 2.48 (s, 3 H) 2.43 - 2.66 (m, 2 H) 2.24 - 2.39 (m, 1 H) 2.18 (s, 3 H) 2.06 - 2.24 (m, 1 H) 1.91 - 2.03 (m, 1 H) 1.77 - 1.89 (m, 1 H) 1.51 - 1.70 (m, 1 H) 1.41 (s, 6 H)

Example 57: *cis*-2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[1-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E57)



To a solution of *cis*- 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[1-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D74,10.5 mg) in dry methanol (1 mL) at 0°C, one drop of concentrated HCl was added. The resulting mixture was stirred at 0°C for 1.5 hours and then was allowed to reach rt and stirred at this temperature for 2 hours. The solution was then directly charged onto a SCX cartridge (eluting with MeOH and ammonia, 0.5N solution in methanol) to give the desired compound (4.5 mg) as yellow oil.
UPLC/MS: peak at Rt = 0.73 min with m/z = 653 $[M+H]^+$.

The following examples were obtained through preparation analogous to the following one:

E58

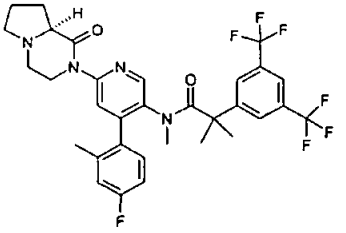
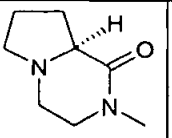
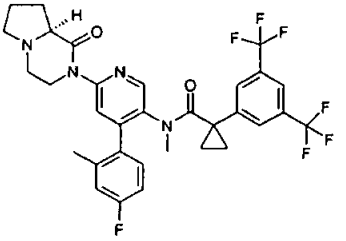
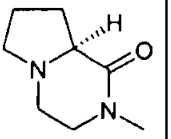
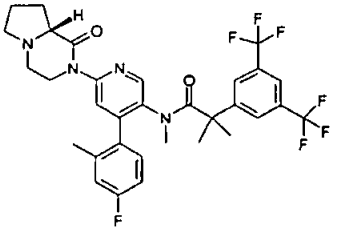
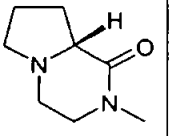
A suspension of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (100 mg),

(8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (D76, 79 mg, 3 eq), CuI (72 mg, 2 eq), N,N'-Dimethylethylenediamine (40 µl, 2 eq) and $CsCO_3$(122.4 mg, 2 eq) in dioxane (3 ml) was heated in a sealed tube at 80°C for 4 hrs and at 120°C overnight. The reaction mixture was taken up with dichloromethane and it was washed with NH_4Cl aq.. The organic phase was evaporated to dryness and the crude was purified by chromatography (silica cartridge, cyclohexane:EtOAc 1:1 to 0:1) to give the title compound (39 mg).

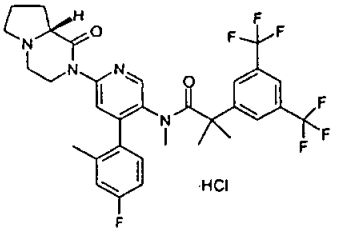
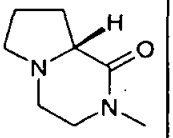
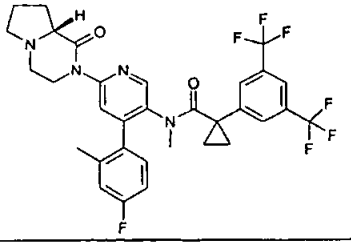
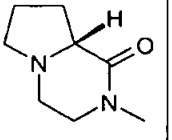
Where prepared, the HCl salts were prepared according to the following experimental procedure:

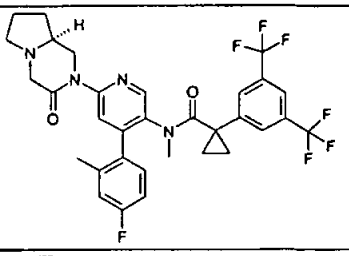
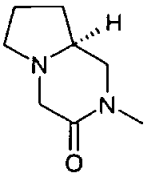
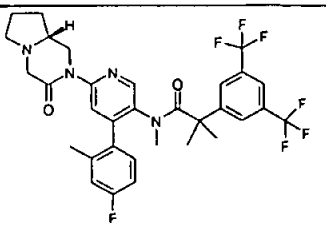
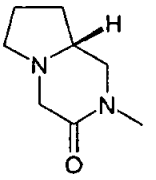
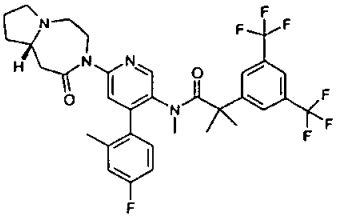
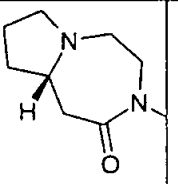
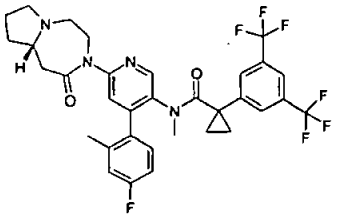
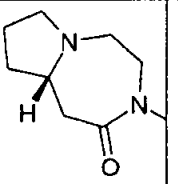
E61

To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(8a*R*)-1-oxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E60, 47 mg, 0.074 mmol) in dichloromethane (1.9 ml), cooled to 0°C, was added dropwise 1N HCl in Et_2O (88 µl) and the reaction mixture was stirred at 0°C for 30 mins. The solvent was evaporated and the solid was triturated with pentane to give title compound (50 mg).

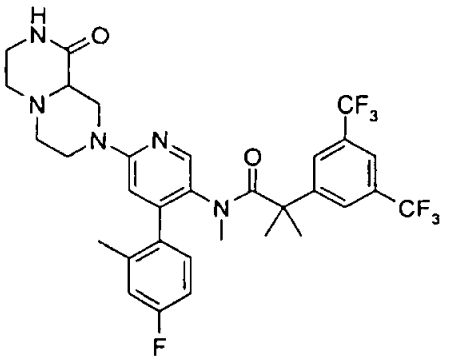
Example n°	Structure	Characterization	Monomer	Monomer Preparation
E58				**Description 76** (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one **(D76)**
E59				The same as before
E60				Described in literature: **Quinolinone compounds.** Jpn. Kokai Tokkyo Koho (1985), 12 pp. CODEN: JKXXAF JP

170

				60166681 A2 19850829 Showa. CAN 104:109495 AN 1986:109495 CAPLUS
E61		1H NMR (500 MHz, DMSO-d_6) δ ppm 11.17 (br. s., 1 H) 8.35 (s, 1 H) 8.04 (s, 1 H) 7.83 (s, 1 H) 7.69 - 7.81 (m, 2 H) 7.22 (d, 1 H) 7.09 - 7.17 (m, 2 H) 3.09 - 4.75 (m, 7 H) 2.45 - 2.56 (m, 3 H) 2.13 (s, 3 H) 1.76 - 2.45 (m, 4 H) 1.11 - 1.71 (m, 6 H)		The same as before
E62				The same as before

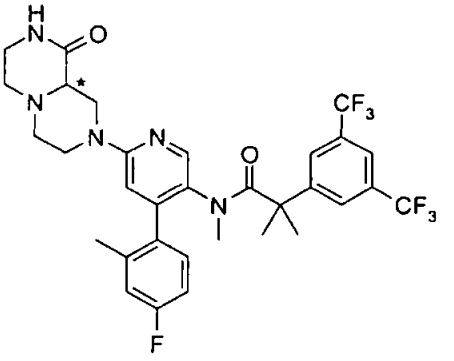
E63				**Description 12** (8a*S*)-Hexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one **(D12)**
E64				**Description 14** (8a*R*)-Hexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one **(D14)**
E65				**Description 5** (9a*S*)-Hexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepin-2(3*H*)-one **(D5)**
E66				**Description 5** (9a*S*)-Hexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepin-2(3*H*)-one **(D5)**

Example 67: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(9-oxooctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide
(E67)



To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (50 mg, 0.092 mmol) in 0.5 mL of DMSO was added hexahydro-2*H*-pyrazino[1,2-*a*]pyrazin-1(6*H*)-one (D78, 33 mg, 0.213 mmol) and potassium carbonate (39 mg, 0.28 mmol) and the reaction was left at 150°C for 24 h. It was worked up by diluting with dichloromethane and extracting with brine. The organics were dried (Na_2SO_4), and the solvent removed. The product was purified by flash chromatography: silica, cyclohexane : EtOAc 50:50 to EtOAc. Obtained 37mg of the title compound.
MS (direct): 652 (M+1)
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.92 (s, 1 H) 7.82 (d, 1 H) 7.66 - 7.78 (m, 2 H) 6.92 - 7.20 (m, 3 H) 6.64 (br. s., 1 H) 4.57 - 4.70 (m, 1 H) 3.25 - 3.32 (m, 1 H) 3.01 - 3.13 (m, 1 H) 2.83 - 2.96 (m, 3 H) 2.52 - 2.68 (m, 2 H) 2.40 (dt, 1 H) 2.01 - 2.31 (m, 8 H) 1.14 - 1.59 (m, 6 H)

Example 68: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*R* *or* 9a*S*)-9-oxooctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E68 - Enantiomer 1)



2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(9-oxooctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E67, 30 mg) was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled 1, of unknown but single stereochemistry was isolated using the following conditions (obtained 8.3 mg, 75%e.e., analytical retention time 15.5 min)

Preparative conditions:

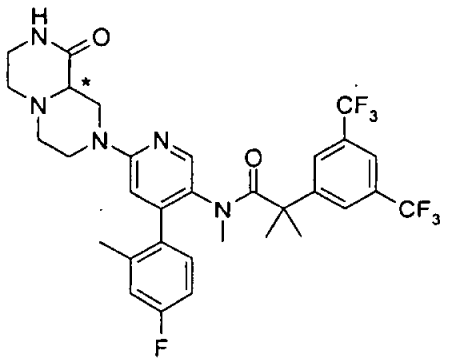
Amount supplied	30 mg
Chiral Column	CHIRALCEL OD-H, (25 x 2.1) cm
Mobile phase	n-Hexane/2-propanol 87/13 % v/v
Flow rate	22 ml/min
P	182 bar
T	36 C
Detection	UV at 220 nm

Analytical SFC (Berger) conditions:

Chiral Column	CHIRALCEL OD-H, (25 x 0.46) cm
Mobile phase	n-Hexane/2-propanol 85/15 % v/v
Flow rate	1.5 ml/min
P	180 bar
T	35 C
Detection	UV at 220 nm

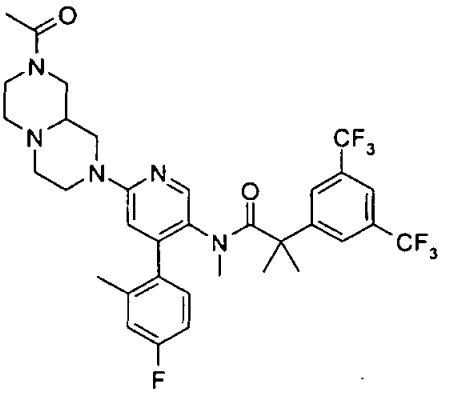
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.03 (s, 1 H) 7.92 (s, 1 H) 7.82 (d, 1 H) 7.50 - 7.78 (m, 2 H) 6.90 - 7.21 (m, 3 H) 6.66 (br. s., 1 H) 4.48 - 4.78 (m, 1 H) 4.05 - 4.21 (m, 1 H) 3.21 - 3.46 (m, 1 H) 3.04 - 3.11 (m, 1 H) 2.79 - 2.96 (m, 3 H) 2.55 - 2.67 (m, 2 H) 2.38 (dd, 1 H) 1.98 - 2.31 (m, 7 H) 1.07 - 1.64 (m, 6 H)

Example 69: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*S* *or* *9aR*)-9-oxooctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E69 - Enantiomer 2)



The title compound was obtained as Enantiomer labeled 2 from the chiral separation of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(9-oxooctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E67), as described for 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*R* *or* *9aS*)-9-oxooctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E68 - Enantiomer 1). Obtained 3.8 mg, >95.5%e.e., analytical retention time 17.7 min).

Example 70: *N*-[6-(8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide
(E70)

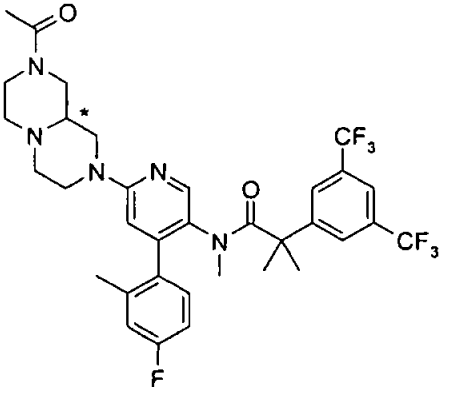


To a solution of crude 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (prepared with an analogous procedure to that described for D80, 89 mg, 0.14 mmol) in 5 mL of dichloromethane were added at 0°C triethylamine (197 µL, 1.41 mmol) and acetyl chloride (75 µL, 1.0 mmol). The reaction was left at room temperature for 2 h. It was diluted with dichloromethane, extracted with sat $NaHCO_3$ solution, the organics dried (Na_2SO_4), and the solvent was removed. The product was purified by flash chromatography (silica, cyclohexane: EtOAc 50:50 to EtOAc). Obtained 60 mg.

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.89 (s, 1 H) 7.61 - 7.83 (m, 2 H) 7.14 (d, 1 H) 6.92 - 7.21 (m, 2 H) 6.65 - 6.80 (m, 1 H) 4.05 - 4.53 (m, 3 H) 3.81 (dd, 1 H) 2.72 - 2.97 (m, 4 H) 2.59 - 2.70 (m, 2 H) 2.50 (s, 3 H) 1.99 (s, 3 H) 1.78 - 2.37 (m, 6 H) 1.01 - 1.56 (m, 6 H)

MS (direct): m/z= 680 (M+1), 340 (2M+2)/2.

Example 71: *N*-[6-[(9a*R* *or* *9aS*)-8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E71- Enantiomer 1)



N-[6-(8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-

dimethylpropanamide (E70, 44.5 mg) was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled 1, of unknown but single stereochemistry was isolated using the following conditions (obtained 12.8 mg, >99.5%e.e., analytical retention time 13.1 min)

Preparative conditions:

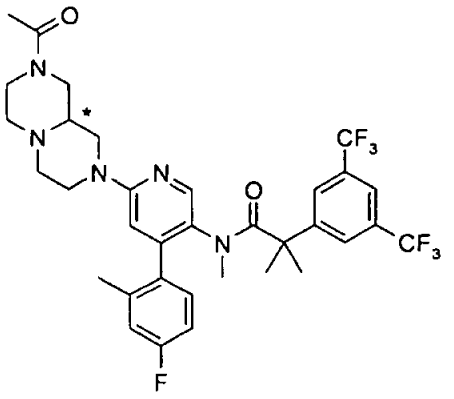
Amount supplied	44.5 mg
Chiral Column	CHIRALCEL OD-H, (25 x 2.1) cm
Mobile phase	n-Hexane/2-propanol 85/15 % v/v
Flow rate	22 ml/min
P	182 bar
T	36 C
Detection	UV at 220 nm

Analytical SFC (Berger) conditions:

Chiral Column	CHIRALCEL OD-H, (25 x 0.46) cm
Mobile phase	n-Hexane/2-propanol 85/15 % v/v
Flow rate	1.5 ml/min
P	180 bar
T	35 C
Detection	UV at 220 nm

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.89 (s, 1 H) 7.61 - 7.83 (m, 2 H) 7.14 (d, 1 H) 6.92 - 7.21 (m, 2 H) 6.65 - 6.80 (m, 1 H) 4.05 - 4.53 (m, 3 H) 3.81 (dd, 1 H) 2.72 - 2.97 (m, 4 H) 2.59 - 2.70 (m, 2 H) 2.50 (s, 3 H) 1.99 (s, 3 H) 1.78 - 2.37 (m, 6 H) 1.01 - 1.56 (m, 6 H)

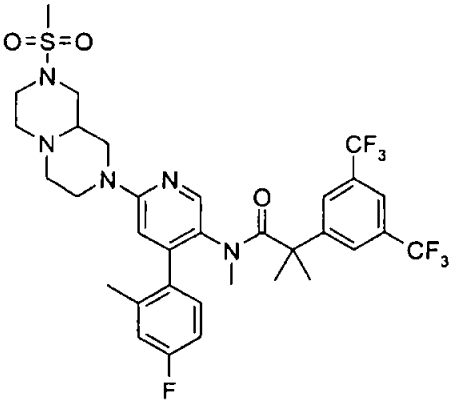
Example 72: *N*-[6-[(9a*S* *or* *9aR*)-8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E72- Enantiomer 2)



The title compound was obtained as Enantiomer labeled 2 from the chiral separation of *N*-[6-(8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E70), as described for *N*-[6-[(9a*R or 9aS*)-8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E71 - Enantiomer 1). Obtained 11.6 mg, >95.5%e.e., analytical retention time 17.5 min)

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.89 (s, 1 H) 7.61 - 7.83 (m, 2 H) 7.14 (d, 1 H) 6.92 - 7.21 (m, 2 H) 6.65 - 6.80 (m, 1 H) 4.05 - 4.53 (m, 3 H) 3.81 (dd, 1 H) 2.72 - 2.97 (m, 4 H) 2.59 - 2.70 (m, 2 H) 2.50 (s, 3 H) 1.99 (s, 3 H) 1.78 - 2.37 (m, 6 H) 1.01 - 1.56 (m, 6 H)

Example 73: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[8-(methylsulfonyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E73)



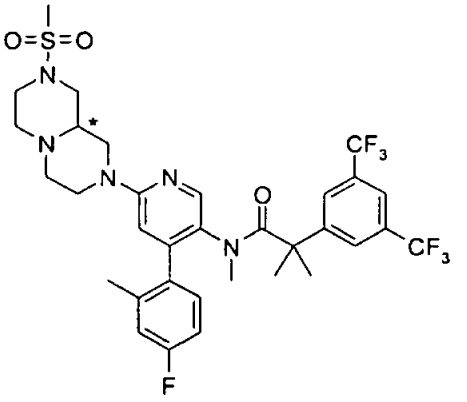
To a solution of crude 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D80, 100 mg, 0.16 mmol) in 5 mL of dichloromethane were added triethylamine (44 µL, 0.32 mmol, 2 eq.) and, at 0°C, methanesulfonyl chloride (18 µL, 0.24 mmol, 1.5 eq.). The reaction was left at room temperature overnight.

Additional 3 eq. of methanesulfonyl chloride were added. It was then diluted with dichloromethane, extracted with sat. $NaHCO_3$, the organics dried (Na_2SO_4), and the solvent was removed. The product was purified by flash chromatography (silica, EtOAc). Obtained 60 mg of the title compound.

MS (direct): m/z= 716 (M+1).

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.89 (s, 1 H) 7.63 - 7.81 (m, 2 H) 6.92 - 7.22 (m, 3 H) 6.77 (s, 1 H) 4.25 - 4.41 (m, 1 H) 4.13 - 4.31 (m, 1 H) 3.51 (d, 1 H) 3.45 (d, 1 H) 2.88 (s, 3 H) 2.81 - 2.92 (m, 2 H) 2.50 (s, 3 H) 2.40 - 2.62 (m, 3 H) 2.18 (s, 3 H) 2.05 - 2.28 (m, 4 H) 1.49 (s, 3 H) 1.35 (s, 3 H)

Example 74: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*R or 9aS*)-8-(methylsulfonyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E74 - Enantiomer 1)



N-[6-(8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E73, 55.5 mg) was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled 1, of unknown but single stereochemistry was isolated using the following conditions (obtained 11.5 mg, >99.5%e.e., analytical retention time 8.16 min)

Preparative conditions:

Amount supplied	55.5 mg
Chiral Column	Chiralpak AD-H, (25 x 2.1) cm
Mobile phase	n-Hexane/Ethanol 60/40 % v/v
Flow rate	13 ml/min

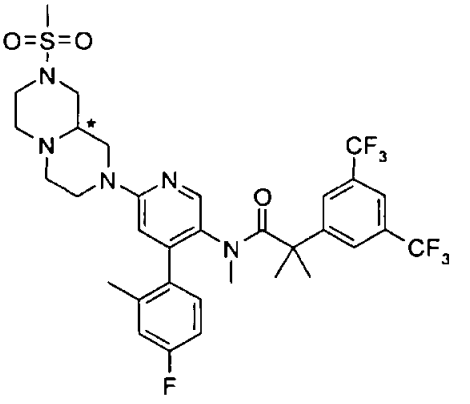
Analytical conditions:

Chiral Column	Chiralpak AD-H, (25 x 0.46) cm
Mobile phase	n-Hexane/Ethanol 60/40 % v/v +1% isopropylamine
Flow rate	0.8 ml/min

Detection	UV 200-400 nm

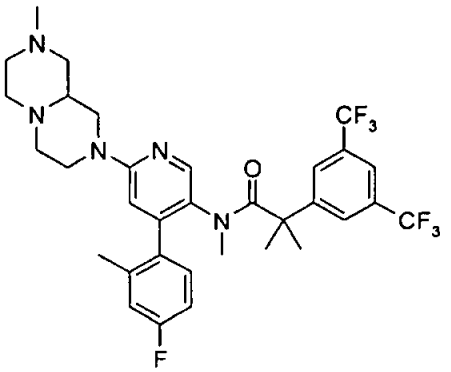
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.90 (s, 1 H) 7.59 - 7.82 (m, 2 H) 6.87 - 7.20 (m, 3 H) 6.68 - 6.84 (m, 1 H) 4.28 - 4.40 (m, 1 H) 4.17 - 4.27 (m, 1 H) 3.52 (d, 1 H) 3.46 (d, 1 H) 2.90 (s, 3 H) 2.80 - 2.93 (m, 4 H) 2.44 - 2.57 (m, 5 H) 2.01 - 2.27 (m, 6 H) 1.24 - 1.60 (m, 6 H)

Example 75: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*S* *or* *9aR*)-8-(methylsulfonyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E75 - Enantiomer 2)



The title compound was obtained as Enantiomer labeled 2 from the chiral separation of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[8-(methylsulfonyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E73), as described for 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*R* *or* *9aS*)-8-(methylsulfonyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E74 - Enantiomer 1). Obtained 12.6 mg, >95.5%e.e., analytical retention time 14.36 min) 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.90 (s, 1 H) 7.59 - 7.82 (m, 2 H) 6.87 - 7.20 (m, 3 H) 6.68 - 6.84 (m, 1 H) 4.28 - 4.40 (m, 1 H) 4.17 - 4.27 (m, 1 H) 3.52 (d, 1 H) 3.46 (d, 1 H) 2.90 (s, 3 H) 2.80 - 2.93 (m, 4 H) 2.44 - 2.57 (m, 5 H) 2.01 - 2.27 (m, 6 H) 1.24 - 1.60 (m, 6 H)

Example 76: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(8-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide
(E76)

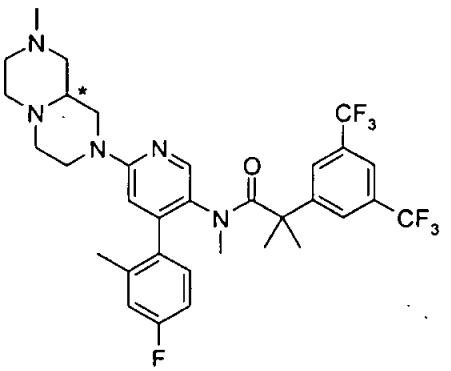


To a solution of crude 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D80, 100 mg, 0.16 mmol) in 5 mL of acetonitrile was added a 37% aqueous formaldehyde solution (24 µL, 0.32 mmol). The solution was stirred at room temperature for 30 min, and then sodium triacetoxyborohydride (50 mg, 0.24 mmol) was added and the reaction stirred at room temperature overnight. The solvent was evaporated and the residue dissolved in dichloromethane and extracted with water and brine. The product was purified by flash chromatography (silica, dichloromethane to dichloromethane: MeOH 95:5). Obtained 58 mg of the title compound.

MS (direct): m/z= 652 (M+1).

1H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 - 8.08 (m, 1 H) 7.81 - 7.93 (m, 1 H) 7.60 - 7.80 (m, 2 H) 7.15 (d, 1 H) 6.88 - 7.12 (m, 2 H) 6.60 - 6.79 (m, 1 H) 4.24 (d, 1 H) 4.12 (d, 1 H) 2.74 - 2.92 (m, 2 H) 2.61 - 2.73 (m, 2 H) 2.41 - 2.57 (m, 4 H) 1.92 - 2.31 (m, 11 H) 1.68 (t, 1 H) 1.10 - 1.56 (m, 6 H)

Example 77: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*S* *or* 9a*R*)-8-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E77 - Enantiomer 1)



N-[6-(8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E76, 50 mg) was submitted for chiral separation to isolate its

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enantiomers. The enantiomer labeled 1, of unknown but single stereochemistry was isolated using the following conditions (obtained 13 mg, 70%e.e., analytical retention time 10.7 min)

Semipreparative SFC (Gilson) conditions:

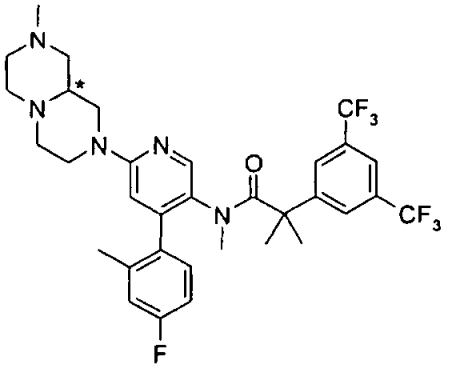
Amount supplied	50 mg
Chiral Column	CHIRALCEL OD-H, (25 x 2.1) cm
Mobile phase	n-Hexane/(Ethanol+0.1% isopropylamine) 95/5 % v/v
Flow rate	22 ml/min
P	182 bar
T	36 C
Detection	UV at 220 nm

Analytical SFC (Berger) conditions:

Chiral Column	CHIRALCEL OD-H, (25 x 0.46) cm
Mobile phase	n-Hexane/2-propanol 85/15 % v/v
Flow rate	1.5 ml/min
P	180 bar
T	35 C
Detection	UV at 220 nm

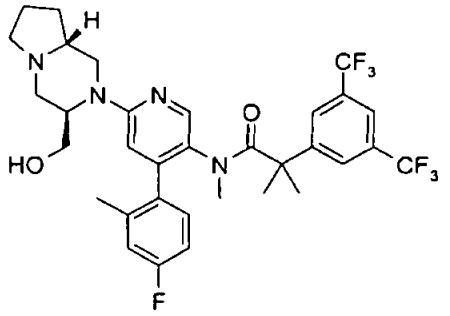
1H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 - 8.07 (m, 1 H) 7.84 - 7.91 (m, 1 H) 7.61 - 7.81 (m, 2 H) 7.16 (d, 1 H) 6.99 - 7.13 (m, 2 H) 6.65 - 6.73 (m, 1 H) 4.24 (d, 1 H) 4.13 (d, 1 H) 2.73 - 2.94 (m, 2 H) 2.62 - 2.75 (m, 2 H) 2.37 - 2.58 (m, 4 H) 1.95 - 2.33 (m, 11 H) 1.69 (t, 1 H) 1.25 - 1.56 (m, 6 H)

Example 78: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*R* *or* 9a*S*)-8-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E78 - Enantiomer 2)



The title compound was obtained as Enantiomer labeled 2 from the chiral separation of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[4-(4-fluoro-2-methylphenyl)-6-(8-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E76), as described for 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(9a*S* *or* *9aR*)-8-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E77 - Enantiomer 1). Obtained 12 mg, >95.5%e.e., analytical retention time 13.9 min).
1H NMR (500 MHz, DMSO-d_6) δ ppm 7.96 - 8.07 (m, 1 H) 7.84 - 7.91 (m, 1 H) 7.61 - 7.81 (m, 2 H) 7.16 (d, 1 H) 6.99 - 7.13 (m, 2 H) 6.65 - 6.73 (m, 1 H) 4.24 (d, 1 H) 4.13 (d, 1 H) 2.73 - 2.94 (m, 2 H) 2.62 - 2.75 (m, 2 H) 2.37 - 2.58 (m, 4 H) 1.95 - 2.33 (m, 11 H) 1.69 (t, 1 H) 1.25 - 1.56 (m, 6 H)

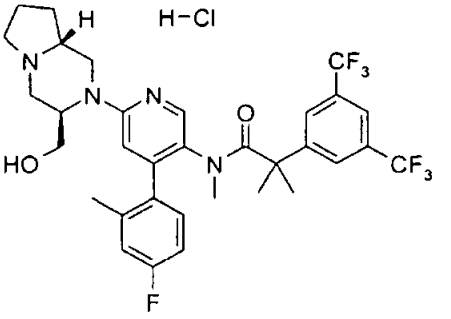
Example 79: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*R*,8a*R*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E79)



(3*R*,8a*R*)-octahydropyrrolo[1,2-*a*]pyrazin-3-ylmethanol (190 mg, 1.22 mmol, Tetrahedron Asymmetry, 1996, 7(7), 1999-2005) was dissolved in 10 mL of toluene, followed by the 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (323 mg, 0.607 mmol), 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (ligand) (57mg, 0.144 mmol), $Pd(dba)_2$ (35 mg, 0.061 mmol) and, at last, cesium carbonate (297 mg, 0.912 mmol).The mixture was stirred at 130°C. After 3.5 h, more ligand (55mg, 0.139 mmol) and $Pd(dba)_2$ (35 mg, 0.061 mmol) were added and the reaction left overnight. It was let cool down to room temperature, diluted with 10 mL of MeOH, loaded on a 10g SCX column, washed with MeOH and eluted with 1M methanolic ammonia. The sample coming from the SCX column was further purified by flash chromatography: 1st column: silica, cyclohexane: EtOAc 50:50 to 0:100; 2nd column, NH2-modified silica, cyclohexane: EtOAc 100:0 to 0:100. Isolated 29 mg of the target material.
O.A.HPLC, peak @ 5.20 min, >99% purity (UV).
LC/MS (checked after 1st column): m/z= 653.

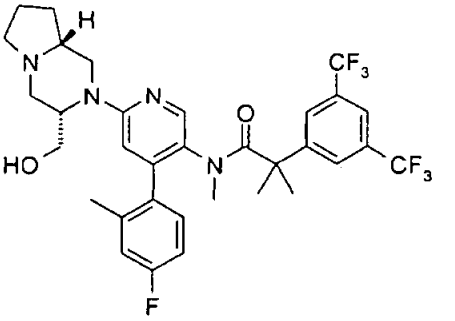
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.85 (s, 1 H) 7.74 (br. s., 2 H) 7.15 (d, 1 H) 7.05 - 7.13 (m, 2 H) 6.53 (s, 1 H) 3.94 - 4.02 (m, 2 H) 3.58 - 3.67 (m, 1 H) 3.53 - 3.59 (m, 1 H) 3.08 - 3.18 (m, 1 H) 2.82 - 2.89 (m, 1 H) 2.72 - 2.80 (m, 1 H) 2.50 - 2.56 (m, 1 H) 2.24 (s, 3 H) 2.15 - 2.19 (m, 1 H) 2.10 (s, 3 H) 1.89 (s, 3 H) 1.73 - 1.83 (m, 1 H) 1.47 (s, 3 H) 1.40 - 1.70 (m, 3 H) 1.34 (s, 3 H)

Example 80 : 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*R*,8a*R*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide Hydrochloride (E80)



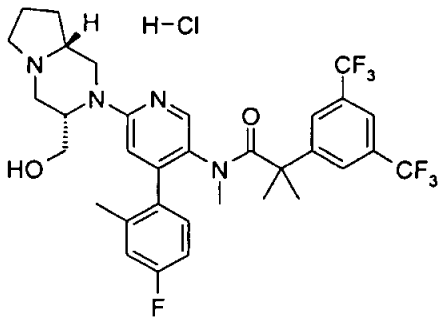
The starting free base (E79, 25 mg, 0.038 mmol) was dissolved in 0.3 mL of dichloromethane and 1M HCl in Et_2O (57 µL, 0.057 mmol) was added at 0°C under a stream of nitrogen. The solution was stirred for 15 min. at 0°C and the solvent was removed under a nitrogen stream. The solid was triturated with Et_2O and pentane, leaving the product as an off-white solid (25 mg).
O.A.HPLC, peak @ 5.20 min, >99% purity (UV).
1H NMR (500 MHz, DMSO-d_6) δ ppm 10.14 (br. s., 1 H) 8.03 (s, 1 H) 7.92 (s, 1 H) 7.75 (br. s., 2 H) 7.17 (d, 1 H) 7.10 (br. s., 2 H) 6.67 (s, 1 H) 5.17 (br. s., 1 H) 4.24 - 4.36 (m, 1 H) 3.48 - 4.04 (m, 6 H) 3.07 - 3.16 (m, 1 H) 2.54 - 2.59 (m, 1 H) 2.24 (s, 3 H) 2.17 (s, 3 H) 2.10 (s, 1 H) 1.97 - 2.06 (m, 1 H) 1.70 - 1.89 (m, 3 H) 1.48 (s, 3 H) 1.34 (s, 3 H)

Example 81: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*S*,8a*R*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E81)



(3*S*,8a*R*)-Octahydropyrrolo[1,2-*a*]pyrazin-3-ylmethanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005, 230 mg, 1.47 mmol) and 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (570 mg, 1.07 mmol) were dissolved in 12 mL of toluene. 2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (ligand) (78 mg, 0.20 mmol), $Pd(dba)_2$ (45 mg, 0.08 mmol) and, at last, caesium carbonate (697 mg, 2.14 mmol) were added. The reaction vessel was sealed and nitrogen bubbled through the solution for 15 min. The reaction mixture was heated to 140°C for 15 h. The mixture was diluted with 100 mL of EtOAc and extracted with water. The aqueous phase was extracted again with dichloromethane. The combined organics were dried and the solvent removed. Product purified by flash chromatography: silica, cyclohexane: EtOAc 50:50 to 0:100. Further purification by HPLC (prep. conditions: Column: Gemini C18 5 µm, 100 x 19 mm; Mobile phase: A: NH4HCO3 sol. 10 mM, pH10; B: CH3CN, Gradient: 50% (B) for 1 min, from 50% (B) to 65% (B) in 12 min, 95% (B) for 6 min; Flow rate: 17 ml/min; UV wavelength range: 210-350 nm; Mass range: 100-900 amu; Ionization: ES+. Isolated 31 mg of the title compound.
O.A.HPLC, peak @ 5.17 min, >99% purity (UV).
LC/MS: m/z= 653 (analytical data from HPLC separation).
1H NMR (300 MHz, DMSO-d_6) δ ppm 7.90 - 8.02 (m, 1 H) 7.82 (s, 1 H) 7.70 - 7.77 (m, 2 H) 7.07 - 7.23 (m, 2 H) 7.03 (td, 1 H) 6.58 (s, 1 H) 4.42 (dd, 1 H) 4.20 - 4.34 (m, 1 H) 3.75 (t, 1 H) 3.49 (dd, 1 H) 3.31 (d, 1 H) 2.97 - 3.17 (m, 1 H) 2.70 (t, 1 H) 2.47 (s, 3 H) 2.17 (s, 3 H) 2.12 - 2.21 (m, 1 H) 1.95 - 2.14 (m, 1 H) 1.86 - 2.07 (m, 1 H) 1.61 - 1.99 (m, 4 H) 1.41 (s, 6 H).

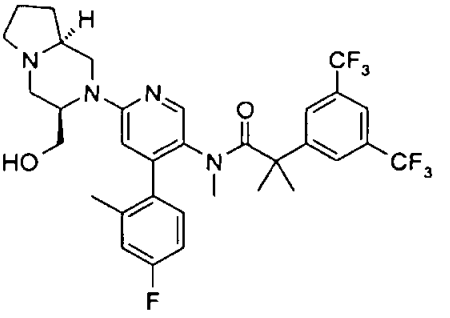
Example 82: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*S*,8a*R*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide Hydrochloride (E82)



2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*S*,8a*R*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E81, 25 mg, 0.038 mmol) was converted to its hydrochloride as reported above in the procedure for 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*R*,8a*R*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-

a]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide Hydrochloride (E80). Obtained 26 mg of the title compound.
O.A.HPLC, peak @ 5.13 min, 98.6% purity (UV).
1H NMR (300 MHz, DMSO-d_6) δ ppm 10.31 (br. s., 1 H) 8.07 (s, 1 H) 7.90 - 7.98 (m, 1 H) 7.63 - 7.87 (m, 2 H) 6.97 - 7.31 (m, 3 H) 6.74 (s, 1 H) 4.48 - 4.95 (m, 2 H) 4.02 - 4.32 (m, 1 H) 2.92 - 4.01 (m, 4 H) 2.27 (s, 3 H) 2.12 (s, 3 H) 1.38 (s, 6 H) 0.66- 2.76 (m, 7 H).

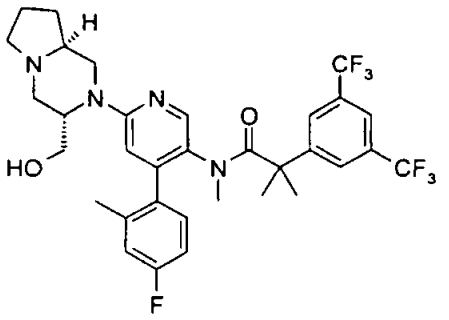
Example 83: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*R*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide
(E83)



To a solution of (3*R*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrrolo[1,2-*a*]pyrazine (D81, 200 mg, 0.739 mmol) in 3 mL of toluene were added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (304 mg, 0.569 mmol) (t-$Bu_3P)_2Pd$ (58 mg, 0.114 mmol), a 25% aqueous solution of cetyltrimethylammonium chloride (35 µL), and, at last, 50% aqueous NaOH (68 µL). The reaction deoxygenated by two freeze-pump-thaw cycles and then heated to 90°C overnight. The solution was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine. The sample was purified by flash chromatography (silica, cyclohexane: EtOAc 95:5 to 60:40). Isolated 230 mg of O-TBDMS protected intermediate (UPLC/MS: pak @ 0.89 min, m/z= 767 (M+1), 384 (M+2)/2).
The intermediate was dissolved in 10 mL of MeOH and 0.5 mL of conc. HCl were added. The reaction was left at room temperature for 1h. The product was isolated by SCX cartridge. Isolated 133 mg of the title compound.
1H NMR (300 MHz, DMSO-d_6) δ ppm 7.90 - 8.02 (m, 1 H) 7.82 (s, 1 H) 7.70 - 7.77 (m, 2 H) 7.07 - 7.23 (m, 2 H) 7.03 (td, 1 H) 6.58 (s, 1 H) 4.42 (dd, 1 H) 4.20 - 4.34 (m, 1 H) 3.75 (t, 1 H) 3.49 (dd, 1 H) 3.31 (d, 1 H) 2.97 - 3.17 (m, 1 H) 2.70 (t, 1 H) 2.47 (s, 3 H) 2.17 (s, 3 H) 2.12 - 2.21 (m, 1 H) 1.95 - 2.14 (m, 1 H) 1.86 - 2.07 (m, 1 H) 1.61 - 1.99 (m, 4 H) 1.41 (s, 6 H).
UPLC/MS: peak @ 0.71 min, m/z= 653 (M+1).

Example 84: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide

(E84)



To a solution of (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrrolo[1,2-*a*]pyrazine (D82, 157 mg, 0.58 mmol) in 2.5 mL of toluene were added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (238 mg, 0.45 mmol) (*t*-$Bu_3P)_2Pd$ (46 mg, 0.09 mmol), a 25% aqueous solution of cetyltrimethylammonium chloride (26 µL), and, at last, 50% aqueous NaOH (54 µL). The reaction deoxygenated by freeze-pump-thaw cycles and then heated to 90°C for 7 h. The reaction was checked by UPLC/MS, showing the expected product peak at 0.84 min, with m/z= 767 (M+1) and 384 ((M+2)/2). The solution was diluted with EtOAc, washed with sat. $NaHCO_3$ and brine. The sample was purified by flash chromatography (silica, cyclohexane: EtOAc 90:10 to 0:100). Isolated 251 mg of O-TBDMS protected intermediate.

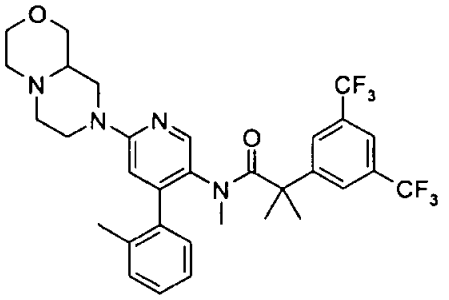
The intermediate was dissolved in 11 mL of MeOH and 0.55 mL of conc. HCl were added. The reaction was left at room temperature for 1h. The product was isolated by SCX cartridge. Isolated 140 mg of the title compound.

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.86 (s, 1 H) 7.75 (br. s., 2 H) 7.15 (d, 1 H) 7.10 (br. s., 2 H) 6.52 (s, 1 H) 4.83 (br. s., 1 H) 3.94 - 4.03 (m, 1 H) 3.57 - 3.69 (m, 1 H) 3.50 - 3.58 (m, 2 H) 3.33 - 3.46 (m, 1 H) 3.18 - 3.27 (m, 1 H) 3.10 - 3.18 (m, 1 H) 2.81 - 2.89 (m, 1 H) 2.73 - 2.81 (m, 1 H) 2.51 - 2.59 (m, 1 H) 2.49 (s, 3 H) 2.11 (s, 3 H) 1.84 - 1.94 (m, 1 H) 1.73 - 1.82 (m, 1 H) 1.55 - 1.68 (m, 1 H) 1.46 (s, 3 H) 1.36 - 1.47 (m, 1 H) 1.33 (s, 3 H)

O.A. HPLC: peak @ 5.20min, 98.9% purity (UV).

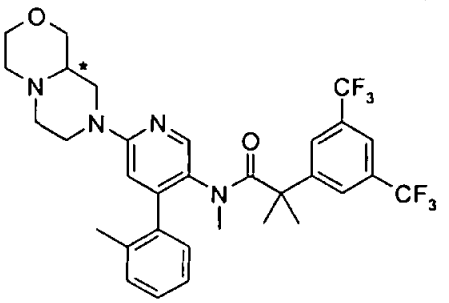
Example 85: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide

(E85)



A solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2002/16324A1] (200 mg, 0.388 mmol), octahydropyrazino[2,1-*c*][1,4]oxazine (EP472826, 111 mg, 0.776 mmol), and potassium carbonate (161 mg, 1.165 mmol) in 1 mL of DMSO was heated to 150°C for 47 h. It was worked up by diluting with dichloromethane and extracting with brine. The organics were dried (Na_2SO_4), and the solvent removed. The product was purified by flash chromatography: silica, dichloromethane to dichloromethane: MeOH 95:5. Obtained 92 mg of the title compound.
HPLC/MS: Peak @ 2.11 min, 621 (M+1)
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.97 (s, 1 H) 7.83 (s, 1 H) 7.69 (br. s., 2 H) 7.23 (s, 2 H) 7.15 (br. s., 1 H) 7.02 (br. s., 1 H) 6.65 (s, 1 H) 4.20 (d, 1 H) 4.04 (d, 1 H) 3.70 (t, 2 H) 3.48 (t, 1 H) 3.09 (t, 1 H) 2.83 (t, 1 H) 2.74 (d, 1 H) 2.62 (d, 1 H) 2.49 (s, 3 H) 2.36 (t, 1 H) 2.09 - 2.24 (m, 3 H) 2.07 (s, 3 H) 1.39 (s, 3 H) 1.25 (s, 3 H).

Example 86: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(9a*R* *or* *9aS*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E86 - Enantiomer 1)



2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E85, 87 mg) was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled 1, of unknown but single stereochemistry was isolated using the following conditions (obtained 41 mg, >99.5%e.e., analytical retention time 5.84 min)

Preparative conditions:

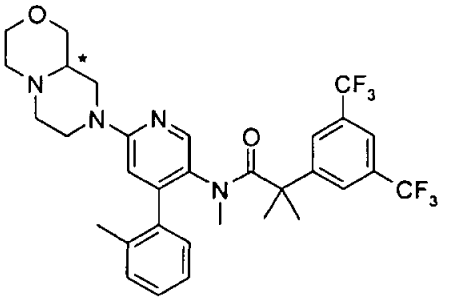
Amount supplied	87 mg
Chiral Column	CHIRALCEL OD-H, (25 x 2.1) cm
Mobile phase	n-Hexane/2-propanol 94/6 % v/v
Flow rate	18 ml/min
Detection	UV at 225 nm

Analytical conditions:

Chiral Column	CHIRALCEL OD-H, (25 x 0.46) cm
Mobile phase	n-Hexane/2-propanol 85/15 % v/v
Flow rate	1.0 ml/min
P	180 bar
T	35 C
Detection	UV at 225 nm

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.87 (s, 1 H) 7.64 - 7.79 (m, 2 H) 6.98 - 7.33 (m, 4 H) 6.64 - 6.74 (m, 1 H) 4.24 (d, 1 H) 4.09 (d, 1 H) 3.74 (t, 2 H) 3.53 (t, 1 H) 3.13 (t, 1 H) 2.86 (t, 1 H) 2.78 (d, 1 H) 2.66 (d, 1 H) 2.51 (s, 3 H) 2.40 (t, 1 H) 2.00 - 2.30 (m, 6 H) 1.11 - 1.48 (m, 6 H).

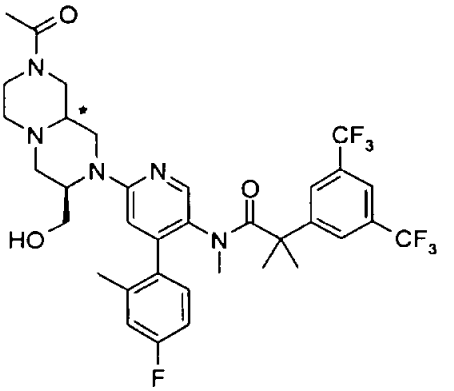
Example 87: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(9a*S* *or* *9aR*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E87 - Enantiomer 2)



The title compound was obtained as Enantiomer labeled 2 from the chiral separation of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E85), as described for 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(9a*R* *or* *9aS*)-hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E86 - Enantiomer 1). Obtained 35 mg of the title compound, >95.5%e.e., analytical retention time 8.80 min.

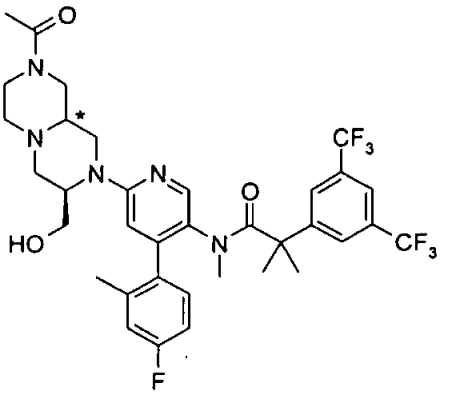
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.87 (s, 1 H) 7.64 - 7.79 (m, 2 H) 6.98 - 7.33 (m, 4 H) 6.64 - 6.74 (m, 1 H) 4.24 (d, 1 H) 4.09 (d, 1 H) 3.74 (t, 2 H) 3.53 (t, 1 H) 3.13 (t, 1 H) 2.86 (t, 1 H) 2.78 (d, 1 H) 2.66 (d, 1 H) 2.51 (s, 3 H) 2.40 (t, 1 H) 2.00 - 2.30 (m, 6 H) 1.11 - 1.48 (m, 6 H).

Example 88: *N*-[6-[(3*R*,9a*R* *or* *9aS*)-8-acetyl-3-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E88 - Diastereoisomer 1)



The *N*-[6-((3*R*,9a*R* *or* *9aS*)-8-acetyl-3-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D88, 148 mg) was dissolved 6 mL of CH_2Cl_2. To this solution was added concentrated HCl (0.3 mL) at 0°C, and stirred at room temperature for 30 min. UPLC/MS analysis showed complete conversion to the expected product (peak at 0.70 min, m/z = 710 (M+1), 355.7 ((M+2)/2)). The reaction mixture was purified by SCX cartridge to give title compound as a solid: 106 mg.
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.88 (s, 1 H) 7.82 (s, 1 H) 7.68 (s, 2 H) 7.03 - 7.13 (m, 2 H) 6.92 - 7.01 (m, 1 H) 6.63 (s, 1 H) 4.40 - 4.47 (m, 1 H) 3.92 - 4.01 (m, 1 H) 3.54 - 3.65 (m, 2 H) 3.51 (dd, 1 H) 3.41 (dd, 1 H) 3.11 (dd, 1 H) 2.72 - 2.81 (m, 1 H) 2.47 (s, 3 H) 2.34 - 2.53 (m, 7 H) 2.11 (s, 3 H) 1.94 (s, 3 H) 1.35 (s, 6 H).

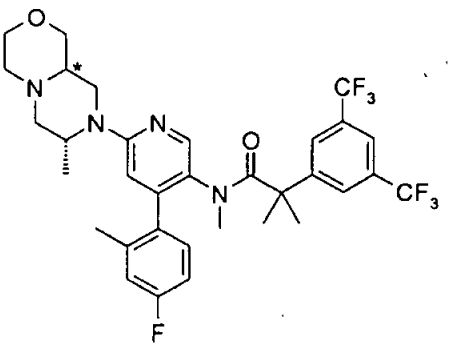
Example 89: *N*-[6-[(3*R*,9a*S* *or* *9aR*)-8-acetyl-3-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E89 - Diastereoisomer 2)



To a solution of the *N*-[6-((3*R*,9a*S* *or* *9aR*)-8-acetyl-3-{[(1,1-dimethylethyl)(dimethyl)silyl]methyl}octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (D92, 199 mg, 0.242 mmol) in 8 mL of MeOH were added dropwise 0.4 mL of conc. HCl. The reaction was stirred at room temperature for 3 h. UPLC/MS analysis showed conversion to the expected product (peak at 0.75 min, m/z = 710 (M+1), 355.7 ((M+2)/2)). The reaction mixture was purified by SCX cartridge to give a solid that was purified further by flash chromatography (silica, dichloromethane to dichloromethane: (0.5 M NH3 in MeOH) 95:5). Obtained 121.6 mg of the title compound.

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.85 (s, 1 H) 7.74 (br. s., 2 H) 7.15 (d, 1 H) 7.10 (br. s., 2 H) 6.61 (br. s., 1 H) 4.67 - 4.73 (m, 1 H) 4.33 (t, 1 H) 4.22 (br. s., 2 H) 3.71 - 3.87 (m, 2 H) 3.37 - 3.45 (m, 1 H) 2.98 - 3.11 (m, 1 H) 2.70 - 2.85 (m, 2 H) 2.53 - 2.69 (m, 2 H) 2.49 (s, 3 H) 2.11 (br. s., 3 H) 2.04 - 2.24 (m, 2 H) 1.99 (s, 3 H) 1.84 - 1.96 (m, 1 H) 1.48 (s, 3 H) 1.33 (s, 3 H).

Example 90: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*,9a*R* *or* *9aS*)-7-methylhexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E90 - Diastereoisomer1)



To a solution of (7*R*,9a*R* *or* *9aS*)-7-methyloctahydropyrazino[2,1-*c*][1,4]oxazine (D94, 50 mg, 0.32 mmol) in 2.1 mL of toluene was added 2-[3,5-

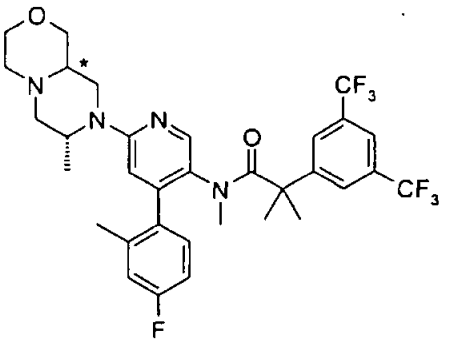
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bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (131 mg, 0.246 mmol), bis-tri –tert-butylphosphine palladium (25 mg, 0.0492 mmol), hexadecyltrimetylammonium chloride (16 μL of a 25% aqueous solution) and, at last, sodium hydroxide solution (29.5 μL of a 50% aqueous solution). The solution was degassed by three freeze-pump-thaw cycles, then stirred at 90°C for 2 h. It was checked by UPLC/MS, which showed peaks for the expected product at 0.75 min. (m/z = 653 (M+1), 327 (M+2)/2). The solution was diluted with EtOAc, extracted with sat. $NaHCO_3$ and dried (Na_2SO_4). The product was isolated by flash chromatography (cyclohexane:EtOAc 70:30 to 0:100, then to EtOAc:MeOH 95:5), obtaining 74 mg of the title compound.

HPLC: Peak @ 5.30 min, 98% purity (UV).

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.03 (s, 1 H) 8.01 (s, 1 H) 7.74 (br. s., 2 H) 7.15 (d, 1 H) 7.10 (br. s., 2 H) 6.77 (s, 1 H) 3.72 (br. s., 1 H) 3.65 (d, 1 H) 3.55 - 3.62 (m, 1 H) 3.53 (t, 1 H) 3.37 - 3.48 (m, 1 H) 3.20 (t, 1 H) 2.94 - 3.01 (m, 1 H) 2.77 - 2.91 (m, 1 H) 2.64 (d, 1 H) 2.59 (br. s., 3 H) 2.40 - 2.46 (m, 1 H) 2.30 - 2.38 (m, 1 H) 2.09 (s, 3 H) 2.03 - 2.13 (m, 1 H) 1.33 (s, 3 H) 1.13 (br. s., 6 H).

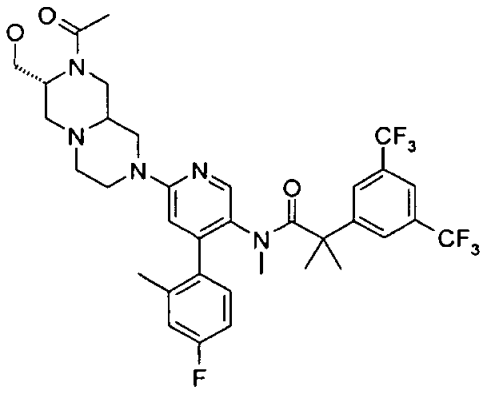
Example 91: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*,9a*S* *or* *9aR*)-7-methylhexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E91 - Diastereoisomer 2).



To a solution of (7*R*,9a*S* *or* *9aR*)-7-methyloctahydropyrazino[2,1-*c*][1,4]oxazine (D95, 28 mg, 0.18 mmol) in 1.2 mL of toluene was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (73.5 mg, 0.138 mmol), bis-tri –tert-butylphosphine palladium (14 mg, 0.028 mmol), hexadecyltrimetylammonium chloride (9 μL of a 25% aqueous solution) and, at last, sodium hydroxide solution (16.5 μL of a 50% aqueous solution). The solution was degassed by three freeze-pump-thaw cycles, then stirred at 90°C for 2 h. It was checked by UPLC/MS, which showed peaks for the expected product at 0.78 min. (m/z = 653 (M+1), 327 (M+2)/2). The solution was diluted with EtOAc, extracted with sat. $NaHCO_3$ and

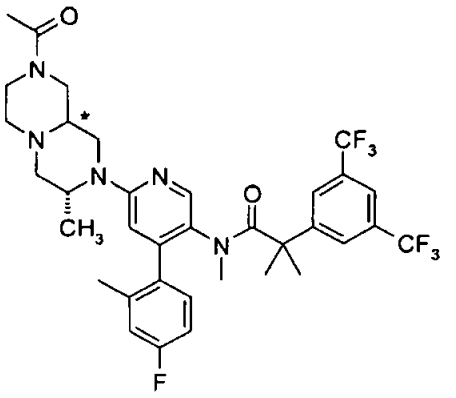
dried (Na_2SO_4). The product was isolated by flash chromatography (cyclohexane:EtOAc 100:30 to 0:100), obtaining 49.6 mg of the title compound.
HPLC: Peak @ 5.35 min, 98% purity (UV).
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.87 (s, 1 H) 7.74 (br. s., 2 H) 7.14 (d, 1 H) 7.10 (br. s., 2 H) 6.60 (br. s., 1 H) 4.49 (br. s., 1 H) 3.89 - 4.01 (m, 1 H) 3.70 - 3.80 (m, 2 H) 3.55 (t, 1 H) 3.17 (t, 1 H) 2.59 - 2.69 (m, 2 H) 2.54 (br. s., 3 H) 2.25 - 2.38 (m, 1 H) 2.23 (br. s., 3 H) 2.00 - 2.19 (m, 3 H) 1.34 (br. s., 3 H) 1.16 (br. s., 3 H) 1.14 (d, 3 H).

Example 92: *N*-[6-[(7*R*)-8-acetyl-7-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E92)



To a solution of {(3*R*)-2-acetyl-8-[5-[{2-[3,5-bis(trifluoromethyl)phenyl]-2-methylpropanoyl}(methyl)amino]-4-(4-fluoro-2-methylphenyl)-2-pyridinyl]octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-3-yl}methyl acetate (D97, 27 mg, 0.0472 mmol) in 2 mL of THF and 0.5 mL of water was added 1M NaOH (1 mL) and the resulting solution was stirred at room temperature for 30 min. It was checked by UPLC/MS, which showed a peak for the expected product at 0.76 min. (m/z = 710 (M+1), 355 (M+2)/2). The target compound was isolated by SCX, obtaining 21 mg of the title compound.
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.88 (s, 1 H) 7.63 - 7.79 (m, 2 H) 6.99 - 7.18 (m, 3 H) 6.76 (s, 1 H) 4.84 (t, 1 H) 4.13 - 4.42 (m, 3 H) 3.78 - 3.91 (m, 1 H) 3.63 - 3.77 (m, 1 H) 3.51 - 3.65 (m, 1 H) 2.72 - 2.95 (m, 2 H) 2.49 (s, 3 H) 2.08 (s, 3 H) 2.03 (s, 3 H) 1.90 - 2.67 (m, 6 H) 1.33 (s, 6 H)
Ratio of Diastereoisomers 1 and 2 not determined.

Example 93: *N*-[6-[(3*R*,9a*R* *or* 9a*S*)-8-acetyl-3-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E93 - Diatereoisomer 1)

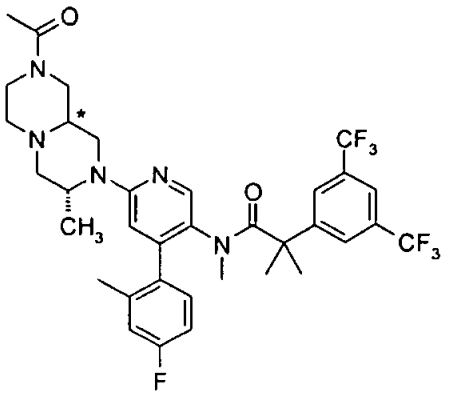


To a solution of (7*R*,9a*R* *or* *9aS*)-2-acetyl-7-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D100, 50 mg, 0.253 mmol) in 1.1 mL of toluene was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (112.6 mg, 0.211 mmol), bis-tri –tert-butylphosphine palladium (27 mg, 0.053 mmol), hexadecyltrimetylammonium chloride (14 μL of a 25% aqueous solution) and, at last, sodium hydroxide solution (25 μL of a 50% aqueous solution). The solution was degassed by three freeze-pump-thaw cycles, then stirred at 90°C for 2.5 h. It was checked by HPLC/MS, which showed a peak for the expected product at 2.07 min. (m/z = 694 (M+1)). The solution was diluted with EtOAc, extracted with sat. $NaHCO_3$ and dried (Na_2SO_4). The product was isolated by flash chromatography (EtOAc to EtOAc: MeOH 90:10), obtaining 138 mg of the title compound.

O.A. HPLC: peak @ 5.20 min, 97% purity (UV).

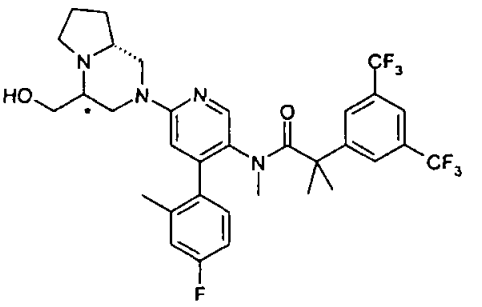
1H NMR (500 MHz, DMSO-d_6) d ppm 8.03 (s, 1 H) 7.98 (s, 1 H) 7.75 (br. s., 2 H) 7.16 (d, 1 H) 7.10 (br. s., 2 H) 6.76 (s, 1 H) 4.16 (d, 1 H) 3.82 - 3.95 (m, 1 H) 3.61 (t, 1 H) 3.48 (br. s., 1 H) 3.14 - 3.26 (m, 1 H) 2.95 - 3.10 (m, 2 H) 2.64 - 2.82 (m, 1 H) 2.50 (br. s., 3 H) 2.43 - 2.61 (m, 1 H) 2.16 - 2.40 (m, 2 H) 2.05 - 2.18 (m, 4 H) 1.97 (s, 3 H) 1.48 (br. s., 3 H) 1.34 (br. s., 3 H) 1.15 (d, 3 H).

Example 94: *N*-[6-[(3*R*,9a*S* *or* *9aR*)-8-acetyl-3-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (E94 - Diastereoisomer 2)



To a solution of (7*R*,9a*R* *or* 9a*S*)-2-acetyl-7-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine and (7*R*,9a*S* *or* 9a*R*)-2-acetyl-7-methyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazine (D100 plus D101, 75 mg, 0.38 mmol) in 1.1 mL of toluene was added 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (169 mg, 0.317 mmol), bis-tri –tert-butylphosphine palladium (40.5 mg, 0.079 mmol), hexadecyltrimetylammonium chloride (20 μL of a 25% aqueous solution) and, at last, sodium hydroxide solution (38 μL of a 50% aqueous solution). The solution was degassed by three freeze-pump-thaw cycles, stirred at 90°C for 6.5 h. It was checked by HPLC/MS, which showed a peaks for the expected products at 1.98 and 2.28 min. (m/z = 694 (M+1)). The solution was diluted with EtOAc, extracted with sat. $NaHCO_3$ and dried (Na_2SO_4). The product was isolated by flash chromatography (dichloromethane to dichloromethane: MeOH 90:10).Obtained 32.4 mg of the title compound.
O.A. HPLC: peak @ 5.25 min, 95% purity (UV).
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.88 (s, 1 H) 7.74 (br. s., 2 H) 7.15 (d, 1 H) 7.10 (br. s., 2 H) 6.61 (br. s., 1 H) 4.52 (br. s., 1 H) 4.34 (t, 1 H) 4.08 (br. s., 1 H) 3.81 (dd, 1 H) 3.28 - 3.35 (m, 1 H) 2.85 (t, 1 H) 2.59 - 2.78 (m, 3 H) 2.50 (br. s., 3 H) 2.10 - 2.38 (m, 2 H) 2.10 (br. s., 3 H) 1.99 (s, 3 H) 1.77 - 1.96 (m, 1 H) 1.48 (br. s., 3 H) 1.33 (br. s., 3 H) 1.16 (d, 3 H).

Example 95 and 96: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(4*S* *or* 4*R*,8a*R*)-4-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E95 – Diastereoisomer 1) 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(4*R* *or* 4*S*,8a*R*)-4-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E96 – Diastereoisomer 2)



To a solution of (8a*R*)-octahydropyrrolo[1,2-*a*]pyrazin-4-ylmethanol (D112, 73 mg, 0.468 mmol) and 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (124 mg, 0.234 mmol) in DMSO (0.75 ml) was added K_2CO_3 (96 mg, 0.702 mmol) and the reaction mixture was stirred for 36 hrs at 120/150°C.

The two diastereoisomers were isolated after purification by SCX and the by chromatography (silica, CH_2Cl_2:MeOH 98:2).

E95- Diastereoisomer 1 (40 mg)

MS: m/z= 653 (M+1) and 327 ($^M/_2$+1)

HPLC: peak @ t=5.22 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.88 (s, 1 H) 7.73 (br. s., 2 H) 7.14 (d, 1 H) 7.10 (br. s., 2 H) 6.63 (br. s., 1 H) 4.62 (s, 1 H) 4.32 - 4.44 (m, 2 H) 3.57 - 3.66 (m, 1 H) 3.30 - 3.36 (m, 2 H) 3.11 - 3.20 (m, 1 H) 2.48 (s, 3 H) 2.41 - 2.58 (m, 2 H) 2.24 (br. s., 1 H) 2.15 (s, 3 H) 2.10 (br. s., 1 H) 1.73 - 1.83 (m, 1 H) 1.60 - 1.70 (m, 4 H) 1.33 (s, 3 H) 1.10 - 1.54 (m, 2 H)

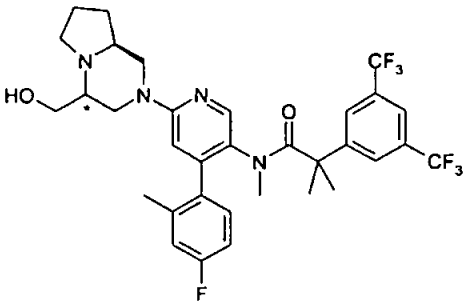
E96- Diastereoisomer 2 (33 mg)

MS: m/z= 653 (M+1) and 327 ($^M/_2$+1)

HPLC: peak @ t=5.152 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.84 (s, 1 H) 7.73 (br. s., 2 H) 7.14 (d, 1 H) 7.10 (br. s., 2 H) 6.51 (s, 1 H) 4.48 - 4.57 (m, 1 H) 3.88 - 3.98 (m, 1 H) 3.48 - 3.61 (m, 3 H) 3.33 - 3.37 (m, 1 H) 3.06 - 3.18 (m, 1 H) 2.81 - 2.94 (m, 3 H) 2.68 - 2.76 (m, 1 H) 2.49 (s, 3 H) 2.11 (s, 3 H) 1.79 - 1.90 (m, 1 H) 1.70 - 1.79 (m, 1 H) 1.56 - 1.69 (m, 1 H) 1.33 (s, 6 H) 1.23 - 1.41 (m, 1 H).

Example 97 and 98: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(4*S* *or* 4*R*,8a*S*)-4-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E97 – Diastereoisomer 1) 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(4*R* *or* 4*S*,8a*S*)-4-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E98 – Diastereoisomer 2)



To 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (375 mg, 0.705 mmol) and K_2CO_3 (389 mg) was added a solution of (8a*S*)-octahydropyrrolo[1,2-*a*]pyrazin-4-ylmethanol (D117, 220 mg, 1.41 mmol) in DMSO (2.3 ml) and the reaction mixture was stirred for 30 hrs at 150°C.

The two diastereoisomers were isolated after purification by SCX and then by chromatography (silica cartridge, CH_2Cl_2:MeOH 98:2).

E97- Diastereoisomer 1 (150 mg):

MS: m/z= 653 (M+1) and 327 ($^M/_2$+1)

HPLC: peak @ t=5.18 min

UPLC/MS: m/z= 653 (M+1) and 327 ($^M/_2$+1) @ t=0.70 min

1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.88 (s, 1 H) 7.73 (br. s., 2 H) 7.14 (d, 1 H) 7.10 (br. s., 2 H) 6.63 (br. s., 1 H) 4.62 (s, 1 H) 4.32 - 4.44 (m, 2 H) 3.57 - 3.66 (m, 1 H) 3.30 - 3.36 (m, 2 H) 3.11 - 3.20 (m, 1 H) 2.48 (s, 3 H) 2.41 - 2.58 (m, 2 H) 2.24 (br. s., 1 H) 2.15 (s, 3 H) 2.10 (br. s., 1 H) 1.73 - 1.83 (m, 1 H) 1.60 - 1.70 (m, 4 H) 1.33 (s, 3 H) 1.10 - 1.54 (m, 2 H)

E98- Diastereoisomer 2 (75 mg):

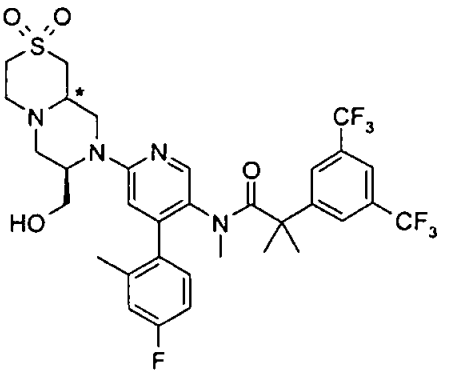
MS: m/z= 653 (M+1) and 327 ($^M/_2$+1)

HPLC: peak @ t=5.15 min

UPLC/MS: m/z= 653 (M+1) and 327 ($^M/_2$+1) @ t=0.72 min

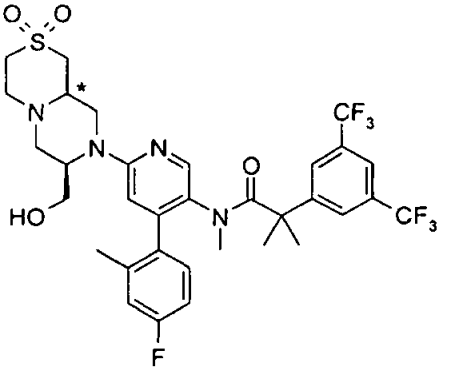
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.84 (s, 1 H) 7.73 (br. s., 2 H) 7.14 (d, 1 H) 7.10 (br. s., 2 H) 6.51 (s, 1 H) 4.48 - 4.57 (m, 1 H) 3.88 - 3.98 (m, 1 H) 3.48 - 3.61 (m, 3 H) 3.33 - 3.37 (m, 1 H) 3.06 - 3.18 (m, 1 H) 2.81 - 2.94 (m, 3 H) 2.68 - 2.76 (m, 1 H) 2.49 (s, 3 H) 2.11 (s, 3 H) 1.79 - 1.90 (m, 1 H) 1.70 - 1.79 (m, 1 H) 1.56 - 1.69 (m, 1 H) 1.33 (s, 6 H) 1.23 - 1.41 (m, 1 H).

Example 99: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*,9a*R* *or* 9a*S*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E99-Diastereoisomer 1)



To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*R*,9a*R or 9aS*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D124, 201 mg, 0.24 mmol) in methanol (8 ml), cooled to 0°C, was added HCl 12 N dropwise (0.47 ml). The reaction mixture was stirred at room temperature for 1 hr, then it was purified by SCX cartridge. The fractions eluted with 2M methanolic ammonia were combined and evaporated to dryness to give the title compound as a white solid (155 mg, y=90%).
HPLC: peak @ t=5.65 min
HPLC/MS: m/z= 717 (M+1) @ t=2.88 min
1H NMR (500 MHz, DMSO-d_6) δ ppm 7.95 - 8.10 (m, 1 H) 7.80 - 7.93 (m, 1 H) 7.59 - 7.81 (m, 2 H) 6.86 - 7.24 (m, 3 H) 6.49 - 6.76 (m, 1 H) 4.63 - 4.79 (m, 1 H) 3.94 - 4.42 (m, 2 H) 3.55 - 3.84 (m, 1 H) 2.86 - 3.52 (m, 7 H) 1.00 - 2.83 (m, 16 H).

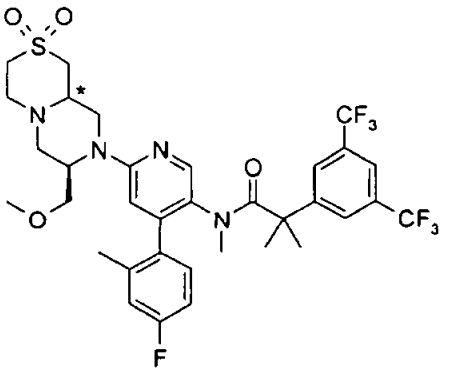
Example 100: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*,9a*S or 9aR*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E100- Diastereoisomer 2)



To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*R*,9a*S or 9aR*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2,2-dioxidohexahydropyrazino[2,1-

c][1,4]thiazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (D125, 127.4 mg, 0.153 mmol) in methanol (5 ml), cooled to at 0°C, was added dropwise HCl 12 N (0.3 ml). The reaction mixture was stirred at room temperature for 2 hrs, then it was purified by SCX cartridge. The fractions eluted with 2M methanolic ammonia were combined and evaporated to dryness to give the title compound as a white solid (104 mg, y=95%).
HPLC: peak @ t=5.54 min
HPLC/MS: m/z= 717 (M+1) @ t=2.91 min
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.85 (s, 1 H) 7.63 - 7.81 (m, 2 H) 7.16 (d, 1 H) 7.03 - 7.17 (m, 2 H) 6.67 (s, 1 H) 4.71 (t, 1 H) 4.19 - 4.36 (m, 1 H) 4.02 - 4.19 (m, 1 H) 3.65 - 3.80 (m, 1 H) 3.36 - 3.53 (m, 1 H) 3.15 - 3.36 (m, 4 H) 3.10 (d, 1 H) 2.86 - 3.01 (m, 1 H) 2.72 - 2.84 (m, 1 H) 2.65 (d, 1 H) 1.10 - 2.56 (m, 14 H).

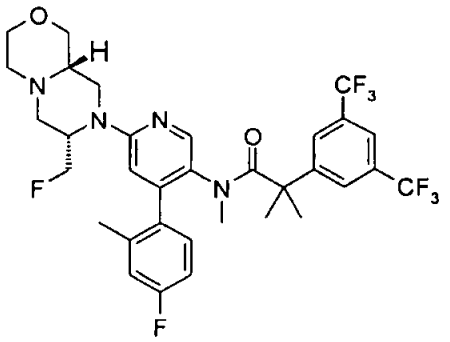
Example 101: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*,9a*R* *or* 9a*S*)-7-[(methyloxy)methyl]-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E101- Diastereoisomer 1)



To a solution of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*,9a*R* *or* 9a*S*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E99, 15 mg, 0.021 mmol) in THF (1 ml) was added under N_2, at r.t., 60% NaH (1 mg, 0.023 mmol) and the reaction mixture was stirred for 30 mins. Then MeI (2 µl, 0.021 mmol) was added and the reaction mixture was stirred for 6 hrs. During this reaction time further amounts of NaH (2 mg, 0.046 mmol) and MeI (4 µl, 0.042 mmol) were added portionwise.
Water was added to the reaction mixture and the aqueous phase was extracted with EtOAc (3X). The combined organic phases were dried and evaporated to dryness. The crude was purified twice by chromatography (silica, CH_2Cl_2:MeOH 1:0 to 8:2 the 1st time and CH_2Cl_2:MeOH 1:0 to 9:1 the 2nd time) to give the title compound (12.4 mg, y=81%)
MS: m/z= 731 (M+1); 753 (M+Na); 366 ($^M/_2$+1)

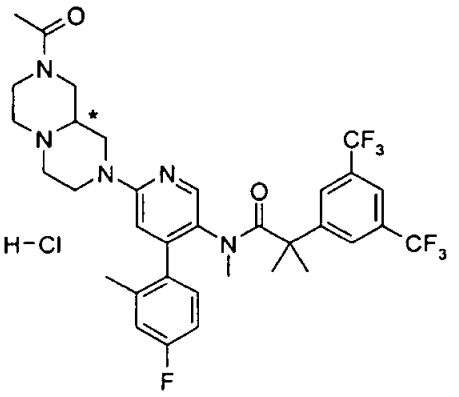
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.87 (s, 1 H) 7.63 - 7.81 (m, 2 H) 7.15 (d, 1 H) 7.02 - 7.19 (m, 2 H) 6.66 (s, 1 H) 4.44 - 4.77 (m, 1 H) 3.99 - 4.27 (m, 1 H) 3.67 (t, 1 H) 3.37 - 3.50 (m, 1 H) 3.23 (s, 3 H) 2.91 - 3.39 (m, 7 H) 2.68 - 2.85 (m, 1 H) 2.51 (s, 3 H) 2.40 - 2.66 (m, 1 H) 2.11 - 2.29 (m, 1 H) 2.11 (s, 3 H) 1.49 (s, 3 H) 1.34 (s, 3 H).

Example 102:
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-[(7*S*,9a*S*)-7-(fluoromethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide (E102)



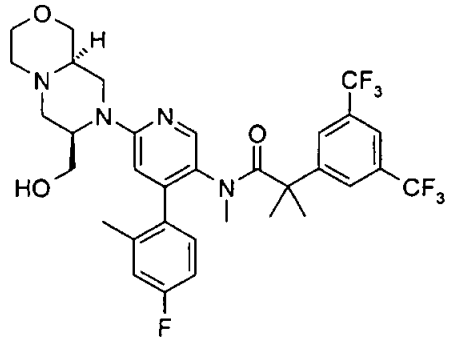
To a solution of (7*S*,9a*S*)-7-(fluoromethyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D129, 14.9 mg, 0.086 mmol) in toluene (1 ml) was added under N_2, at r.t., 2-chloropyridine (35 mg, 0.066 mmol) and then hexadecyltrimetylammonium chloride (4 μL of a 25% aqueous solution), bis-tri–tert-butylphosphine palladium (7 mg), and sodium hydroxide solution (8 □L of a 50% aqueous solution). The reaction mixture was degassed by freeze-pump-thaw cycles and then it was stirred at 90°C for 1 hr. EtOAc and $NaHCO_3$ were added to the reaction mixture, the two phases were separated and the aqueous phase was extracted with EtOAc (3X). The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The crude was purified by chromatography (silica, cyclohexane:EtOAc 7:3 to 0:1) to give the title compound as a brownish foam (30 mg, y=68%).
UPLC/MS: m/z= 671 (M+1) @ t=0.93 min
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1 H) 7.88 (s, 1 H) 7.60 - 7.80 (m, 2 H) 6.99 - 7.23 (m, 3 H) 6.69 (s, 1 H) 4.66 - 4.89 (m, 1 H) 4.56 - 4.73 (m, 1 H) 3.96 - 4.09 (m, 1 H) 3.67 - 3.79 (m, 2 H) 3.54 (t, 1 H) 3.14 (t, 1 H) 2.89 (d, 1 H) 2.49 - 2.69 (m, 1 H) 2.50 (s, 3 H) 2.04 - 2.38 (m, 2 H) 2.09 (s, 3 H) 1.53 - 1.74 (m, 1 H) 1.34 (s, 6 H) 1.11 - 1.46 (m, 1 H) 1.03 - 1.43 (m, 1 H).

Example 103 HCl: *N*-[6-[(9a*R* *or* 9a*S*)-8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide hydrochloride (E103-Enantiomer 2)



To a solution of *N*-[6-(8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl)-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide, enantiomer 2 (E72, 19 mg, sample from a different preparation having comparable analytical characteristics to the reported one) in diethyl ether at 0°C were added 33.5 µL of a 1M HCl solution in diethyl ether. The solution was stirred for 10 minutes and the solvent was removed under a nitrogen stream. The residue was triturated with diethyl ether and pentane and collected by filtration. Obtained 20 mg of the target compound.
1H NMR (500 MHz, DMSO-d_6) δ ppm 10.27 - 10.61 (m, 1 H) 8.04 (s, 1 H) 7.94 (s, 1 H) 7.62 - 7.81 (m, 2 H) 7.17 (d, 1 H) 7.04 - 7.16 (m, 2 H) 6.86 (s, 1 H) 4.44 - 4.76 (m, 3 H) 3.97 - 4.26 (m, 1 H) 2.73 - 3.91 (m, 7 H) 2.48 (s, 3 H) 2.09 - 2.54 (m, 2 H) 2.11 (s, 3 H) 2.05 (s, 3 H) 1.49 (s, 3 H) 1.38 (s, 3 H).

Example 104: 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*R*,9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide (E104)



(7*R*,9a*R*)-7-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)octahydropyrazino[2,1-*c*][1,4]oxazine (D132, 85 mg, 0.297 mmol) was dissolved in 1 mL of toluene by stirring at room temperature. Additional 1 mL of toluene was added to obtain complete dissolution. A sample of 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-[6-chloro-4-

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(4-fluoro-2-methylphenyl)-3-pyridinyl]-*N*,2-dimethylpropanamide [WO 2005/002577] (143 mg, 0.268 mmol) was added, followed by a solution of 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (ligand) (13 mg, 0.033 mmol) and $Pd(dba)_2$ (8 mg, 0.014 mmol) in 1 mL of toluene. Potassium tert-butoxide (39 mg, 0.406 mmol) was added and the reaction vessel closed, evacuated and back-filled with argon. The mixture was reacted under microwave irradiation at 140°C for 15 min. and then for additional 30 min. The mixture was diluted with 30 mL of EtOAc and extracted sat. $NaHCO_3$, dried (Na_2SO_4) and the solvent removed. Product purified by flash chromatography: silica, cyclohexane: EtOAc 100:0 to 80:20. Obtained a partially purified sample: analyzed by UPLC/MS (purity: 24% by UV trace, 58% by MS trace), used directly in the deprotection step. UPLC/MS: peak @ 1.21 min, m/z= 783 (M+1), 392 (M+2/2).
The intermediate (55 mg) was dissolved in 2 mL of methanol and added 0.1 mL of conc. HCl. The solution was stirred at room temperature for 1h. It was loaded on a SCX cartridge, washed with MeOH, and the product was eluted with 1 M ammonia in MeOH. UPLC/MS analysis showed the expected product peak at 0.75 min (m/z= 669, M+1; 335, (M+2)/2). It was purified further by flash chromatography (silica, cyclohexane: EtOAc 50:50 to 0:100). Obtained 12 mg.
1H NMR (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1 H) 7.84 (s, 1 H) 7.74 (br. s., 2 H) 7.15 (d, 1 H) 7.10 (br. s., 2 H) 6.60 (s, 1 H) 4.65 - 4.75 (m, 1 H) 4.22 (br. s., 1 H) 4.08 (br. s., 1 H) 3.68 - 3.80 (m, 3 H) 3.53 (t, 1 H) 3.34 - 3.43 (m, 1 H) 3.14 (t, 1 H) 3.01 (d, 1 H) 2.63 (d, 1 H) 2.48 (s, 3 H) 2.17 (s, 3 H) 2.00 - 2.29 (m, 4 H) 1.46 (s, 3 H) 1.34 (s, 3 H)

Biological Data

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

Measurement of NK binding affinity

The NK binding affinity of the compounds in the invention was determined using the following scintillation proximity assay (SPA) (see H. M. Sarau *et al*, J. Pharmacol. Experimental Therapeutics 1997, 281(3), 1303-1311; H. M. Sarau *et al*, J. Pharmacol. Experimental Therapeutics 2000, 295(1), 373-381; G. A. M. Giardina et al J.Med.Chem 1999, 42, 1053-1065). ^{125}I-Substance P, ^{125}I-NKA and ^{125}I-[MePhe7]-NKB were used in the binding SPA of NK1, NK2 and NK3 receptor, respectively. Polystyrene Leadseeker WGA-SPA beads (Amersham Biosciences) were mixed with plasma membrane prepared from CHO cell lines expressing NK1, NK2 or NK3 in a bead/membrane ratio of 20:1 (w/w) in assay buffer (75mM Tris pH 7.8, 75mM NaCl, 4mM $MnCl_2$, 1mM EDTA, 0.05% Chaps, 1mM PMSF). The mixture was placed on ice for 20 minutes to allow the formation of membrane/bead complex before BSA was added to a final concentration of 1%. After another 20 minutes of incubation on ice, the bead/membrane complex was washed twice and suspended in assay buffer. ^{125}I-labelled ligands were then added to the

bead/membrane complex. 10 µl of the resulting mixture was then dispensed into each well of a low volume Greiner 384-well plate with 100 nL compound pre-dispensed in 100% DMSO. The plates were then sealed and pulse spun at 1100 rpm. After 2-3 hours incubation at room temperature with shaking, the plates were spun for 2 min at 1100 rpm and measured in Viewlux imager (PerkinElmer) for 5 minutes with a 618-nm filter. Inhibition of radioactive ligand binding to its respective receptor was measured by the reduction of signal. pK_i was calculated using K_d of each radioactive ligand determined in a separate experiment.

Measurement of NK functional affinity:

Calcium mobilization assay in (FLIPR): Bacman expressed NK receptors

Compounds of the invention were further characterised in a functional assay using FLIPR technology for the determination of their effect to inhibit the intracellular calcium release induced by interaction of NK receptors with its perspective ligands. Human U2OS cells transiently transduced with recombinant BacMan virus expressing NK1, NK2 and NK3 receptors were used in the studies (see J. P. Condreay *et al*, Proc. Natl. Acad. Sci. USA 1999, 96(1): 127-132). Briefly, U2OS cells were harvested from tissue culture flasks, re-suspended to a cell density of 200-300K/ml and mixed with recombinant BacMan virus carrying NKR gene in a virus/cell ratio of 1% (v/v). 10K-15K cells/well were then seeded in 384-well Greiner bio-one plate in culture medium (DMEM with 10% FBS), incubated overnight in CO_2 at 37°C. After aspirating the medium, cells were loaded 18-24 hr later with cytoplasmic calcium indicator Calcium 3 dye (Molecular Devices Co.) in 30uL/well buffer (Hank's balanced salts with 20 mM Hepes) and incubated in CO_2 at 37°C for 60 minutes. 10uL/well assay buffer (Hank's balanced salts with 20 mM Hepes) containing different concentrations of compounds were then added to the cells for 30 minutes incubation at 37°C. Finally, 10uL/well of NKR ligands in assay buffer containing 0.1% BSA was added to the cells and fluorescence signal read on a FLIPR system. Substance P, NKA and NKB peptides were used as the ligands for NK1, NK2 and NK3 receptor, respectively. IC50 values of each compound were determined by an 11-point 3X-dilution inhibition curve. The potency each antagonist (fpK_i) was calculated from pIC50 by the Cheng-Prusoff equation using EC50 of ligand determined in a separate experiment.

Measurement of NK3 functional affinity

Calcium mobilization assay in (FLIPR): stably expressed NK receptors

Human cloned neurokinin 3 (NK_3) receptors stably expressed in human embryonic kidney (HEK 293) cells were maintained in Minimum Essential Medium (MEM, 31095-029 Invitrogen Life Technologies, Paisley, UK) supplemented with 5 % foetal bovine serum, 1% L-glutamine and 400-500 µg geneticin and were sub-cultured using Accutase (PAA Labs, Austria). Cells were maintained at 37°C 5% CO_2/O_2 in a humidified incubator. Changes in intracellular Ca^{2+} were determined using a Fluorescence Imaging Plate Reader (FLIPR) (Molecular Devices, Sunnyvale CA, USA) by a method similar to that described by Jerman *et al*, (2001). HEK 293 cells stably expressing the human NK_3 receptor were seeded into

black walled, clear-base poly-d-lysine coated 96 well plates (Costar, UK) at a density of 25,000 cells per well incubated overnight. Cells were incubated (37°C for 60 min) with Calcium Plus Reagent (Molecular Devices) in Tyrodes buffer (NaCl, 145 mM; KCl, 2.5 mM; HEPES, 10 mM; Glucose, 10 mM; $MgCl_2$, 1.2 mM; $CaCl_2$, 1.5 mM) containing probenecid (2.5 mM), before incubation (30 min at 37°C) with either buffer or antagonist (50 µl). The plates were then placed on the FLIPR and 50 µl NKB was added (10pM – 1 µM final concentration) changes in fluorescence were monitored. Peak changes in fluorescence occurred within the first 5 sec and were reported following baseline subtraction. Concentration-response curves were analysed using a 4-parameter logistic equation (GraphPad Prism, GraphPad Software Inc.) to obtain pEC_{50} values (-log EC_{50}), pA_2 values were obtained by Schild analysis. Data are the mean ± s.e.mean of three separate experiments.

[^{3}H] Inositol Phosphates Accumulation Assay

[^{3}H] Inositol phosphates accumulation was measured using the methodology of Brandish *et al.*, (2003). Briefly, human osteosarcoma cells (U-2OS cells) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) with 10% foetal calf serum. Cells were maintained at 5% CO_2/O_2 in a humidified incubator at 37°C. All cell culture reagents were obtained from Invitrogen, Paisley, UK. U-2OS cells were grown to confluence, harvested and suspended in growth media at a density of 250000 cells per mL. Human NK_3 Bacmam virus was then added at a concentration of 50 plaque forming units per cell. 25000 cells per well were seeded into black walled clear-base 96 well plates (Corning Costar, UK) incubated overnight.

Following aspiration of growth media, cells were washed with 2 x 200 µL inositol free (IF) assay medium, 3% bovine serum albumin, 2 µM L-Glutamine. The cells were incubated for 16 h with inositol-free DMEM in the presence of [^{3}H]-myo-inositol 1 µCi per well (Amersham U.K).

Growth media was then aspirated and the cells washed with 2 x 200 µL IF DMEM. The cells were pre-incubated (30 min, 37°C) in the absence or presence of test compounds before the addition of various concentrations of NKB (0.1nM – 10mM) in the presence of LiCl (5 mM). After 30 min incubation with the agonist, the assay was terminated by aspiration of the assay media and the addition of 200 uL 0.1 M formic acid to the cells. Following an hour incubation, 20 uL aliquots were mixed with 80 uL of yttrium silicate beads into solid white pico-plates (PerkinElmer). Plates were agitated gently for 1h before allowing the bead mixture to settle for 2h. Plates were counted on TopCount (PerkinElmer). Data is presented as a percentage of the maximal NKB response. Concentration-response curves were analysed using a 4-parameter logistic equation (GraphPad Prism, GraphPad Software Inc.) pA_2 values were obtained by Schild analysis. Data are the mean ± s.e.mean of three separate experiments.

Results

The compounds of Examples E1 to E33 were tested in the NK1 binding affinity assay and exhibited binding affinity > 8.0 pK_i.

The compounds of Examples E34-E40 and E72 exhibited binding affinity in the NK1 binding affinity assay > 8.5 pK_i

The compounds of Examples E41-E71 and E73-E104 exhibited binding affinity in the NK1 binding affinity assay > 8.0 pK_i

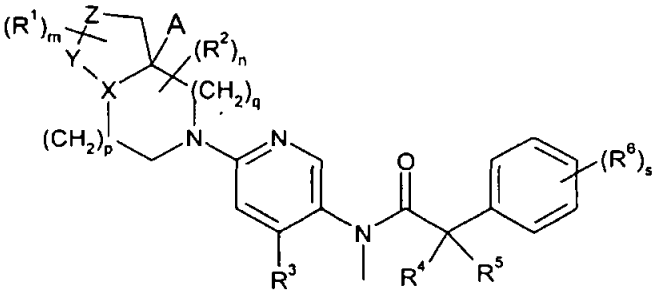
The compounds of Examples E1 to E33 were also tested in the NK3 binding affinity assay and exhibited binding affinity > 5.5 pK_i.

The compounds of Examples E34-E40 and E72 exhibited binding affinity in the NK3 binding affinity assay ≥ 8.0 pK_i.

The compounds of Examples E41-E71 and E73-E104 exhibited binding affinity in the NK3 binding affinity assay > 5.0 pK_i.

CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X represents a nitrogen atom;

Y represents $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ or $-C(=O)-$;

Z represents $-C(H_2)-$, $-S(O_2)-$, $-N(R^z)-$, or an oxygen or sulphur atom;

A represents hydrogen or $-CH_2OH$;

R^z represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-COR^7$ or $-SO_2R^7$;

R^1 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, =O, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, hydroxyl or $-CH_2OH$;

m represents an integer from 0 to 3;

R^2 represents halogen, =O, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), $-COOR^7$, $-CONR^7R^8$, C_{1-6} alkoxy, haloC_{1-6} alkyl, haloC_{1-6} alkoxy or C_{1-6}alkylOC_{1-6}alkyl;

n represents an integer from 0 to 3;

p and q independently represent an integer from 0 to 2;

R^3 represents an –aryl, -heteroaryl, -heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or –heterocyclyl-heterocyclyl group, all of which may be optionally substituted by one or more (e.g. 1, 2 or 3) halogen, C_{1-6} alkyl (optionally substituted by one or more hydroxyl groups), C_{3-8} cycloalkyl, C_{1-6} alkoxy, hydroxyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, cyano, $-S-C_{1-6}$ alkyl, $-SO-C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, $-NR^7COC_{1-6}$ alkyl, $-NR^7SO_2-C_{1-6}$ alkyl, C_{1-6} alkyl-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ or $-SO_2NR^7R^8$ groups;

R^4 and R^5 independently represent C_{1-6} alkyl, or R^4 and R^5 together with the carbon atom to which they are attached may together form a C_{3-8} cycloalkyl group;

R^6 represents halogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;

s represents an integer from 0 to 4;

R^7 and R^8 independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

or solvates thereof.

2. A compound according to claim 1 wherein p and q both represent 1, X represents a nitrogen atom, Y represents -C(H_2)- and Z represents -C(H_2)-.

3. A compound according to claim 1 wherein p and q both represent 1, X represents a nitrogen atom, Y represents (-C(H_2)-)$_2$ and Z represents an oxygen atom.

4. A compound according to claim 1 wherein p and q both represent 1, X represents a nitrogen atom, Y represents -S(O_2)- and Z represents -C(H_2)-.

5. A compound according to claim 1 wherein p and q both represent 1, X represents a nitrogen atom, Y represents -C(=O)- and Z represents -C(H_2)-.

6. A compound according to claim 1 wherein p represents 1, q represents 2, X represents a nitrogen atom, Y represents -C(H_2)- and Z represents -C(H_2)-.

7. A compound according to claim 1 wherein p represents 2, q represents 1, X represents a nitrogen atom, Y represents -C(H_2)- and Z represents -C(H_2)-.

8. A compound according to claim 1 wherein p and q both represent 1, X represents a nitrogen atom, Y represents (-C(H_2)-)$_2$ and Z represents -S(O_2)-.

9. A compound according to claim 1 wherein p and q both represent 1, X represents nitrogen, Y represents (-C(H_2)-)$_2$ and Z represents –N(R^z)-.

10. A compound according to claim 1 wherein p represents zero, q represent 1, X represents nitrogen, Y represents -C(H_2)- and Z represents -C(H_2)-.

11. A compound according to any of claims 1 to 10 wherein m represents 0 or 1.

12. A compound according to any of claims 1 to 11 wherein n represents 0 or 1.

13. A compound according to any of claims 1 to 12 wherein R^1 represents =O, hydroxyl, -CH_2OH.

14. A compound according to any of claims 1 to 13 wherein R^2 represents =O, C_{1-6} alkyl, C_{1-6}alkylOC_{1-6}alkyl, haloC_{1-6} alkyl or C_{1-6} alkyl substituted by a hydroxyl group.

15. A compound according to any of claims 1 to 14 wherein A represents hydrogen or –CH_2OH.

16. A compound according to any of claims 1 to 15 wherein R^7 represents C_{1-6}alkyl.

17. A compound according to any of claims 1 to 16 wherein Z represents $-N(R^z)-$ and R^z represents hydrogen, C_{1-6} alkyl, $-COR^7$, or $-SO_2R^7$.

18. A compound according to claim 17 wherein R^7 represents C_{1-6}alkyl.

19. A compound according to any of claims 1 to 18 wherein R^3 represents –aryl mono substituted by a halogen or C_{1-6} alkyl group, –aryl di substituted by a halogen and C_{1-6} alkyl group, –aryl monosubstitued by C_{1-6}alkyl substituted by one or more hydroxyl groups, –aryl di substituted by a halogen, –heteroaryl monosubstitued by C_{1-6}alkyl or –heteroaryl di substituted by a halogen and a C_{1-6} alkyl group.

20. A compound according to any of claims 1 to 19 wherein R^4 and R^5 both represent C_{1-6} alkyl or R^4 and R^5 together with the carbon atom to which they are attached together form a C_{3-8} cycloalkyl group.

21. A compound according to any of claims 1 to 20 wherein s represents 2 and both R^6 groups are haloC_{1-6} alkyl.

22. A compound according to claim 1 wherein p and q both represent 1, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$, Z represents an oxygen atom, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, R^3 represents –aryl di substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl and s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl.

23. A compound according to claim 1 wherein p and q both represent 1, X represents a nitrogen atom, Y represents $(-C(H_2)-)_2$, Z represents $-S(O_2)-$, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, R^3 represents –aryl di substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl and s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl.

24. A compound according to claim 1 wherein p and q both represent 1, X represents nitrogen, Y represents $(-C(H_2)-)_2$, Z represents $-N(R^z)-$, n represents 1, R^2 represents C_{1-6} alkyl substituted by a hydroxyl group, R^3 represents –aryl di substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl and s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl.

25. A compound according to claim 1 wherein p and q both represent 1, n and m both represent 0, A represents hydrogen, X represents nitrogen, Y represents $(-C(H_2)-)_2$, Z represents $-N(R^z)-$, R^3 represents –aryl substituted by a halogen and C_{1-6} alkyl group, R^4 and R^5 both represent C_{1-6} alkyl, s represents 2 wherein both R^6 groups are haloC_{1-6} alkyl and R^z represents $-COR_7$, wherein R_7 is C_{1-6}alkyl.

26. A compound according to claim 1 which is a compound of formula E1-E104 or a pharmaceutically acceptable salt thereof.

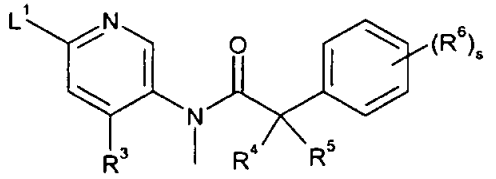
27. A compound according to claim 1 selected from the group consisting of:
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*S*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*)-7-(hydroxymethyl)-2,2-dioxidohexahydropyrazino[2,1-*c*][1,4]thiazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide,
N-[6-[(3*S*)-8-acetyl-3-(hydroxymethyl)octahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide,
or a pharmaceutically acceptable salt thereof.

28. A compound according to claim 1 which is:
2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9a*R*)-7-(hydroxymethyl)hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide or a pharmaceutically acceptable salt thereof.

29. A compound according to claim 1 which is:
N-[6-[(9a*S* *or* *9aR*)-8-acetyloctahydro-2*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-4-(4-fluoro-2-methylphenyl)-3-pyridinyl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide (Enantiomer 2) or a pharmaceutically acceptable salt thereof, wherein "Enantiomer 2" means a single enantiomer of unknown absolute stereochemistry prepared according to Example 72 described herein.

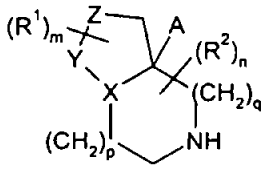
30. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any of claims 1 to 29, which process comprises:

(a) reacting a compound of formula (II)



(II)

wherein R^3, R^4, R^5, R^6 and s are as defined above and L^1 represents a suitable leaving group such as a halogen atom (e.g. chlorine), with a compound of formula (III)



(III)

or an optionally protected derivative thereof, wherein R^1, R^2, m, n, p, q, X, Y, Z and A are as defined above; optionally thereafter followed by

(b) deprotecting a compound of formula (I) which is protected; and

(c) interconversion to other compounds of formula (I).

31. A pharmaceutical composition which comprises the compound of formula (I) as defined in any of claims 1 to 29 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

32. A compound as defined in any of claims 1 to 29 for use in therapy.

33. A compound as defined in any of claims 1 to 29 for use in the treatment of psychotic disorders.

34. Use of a compound as defined in any of claims 1 to 29 in the manufacture of a medicament for the treatment of psychotic disorders.

35. A method of treatment of psychotic disorders which comprises administering to a host in need thereof an effective amount of a compound of formula (I) as defined in any of claims 1 to 29 or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition for use in the treatment of psychotic disorders which comprises the compound of formula (I) as defined in any of claims 1 to 29 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/008845

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D513/04 C07D487/04 C07D498/04 A61K31/4985 A61K31/5383
A61K31/542 A61K31/4439 A61K31/551 A61P25/00

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/002577 A (HOFFMANN LA ROCHE [CH]; HOFFMANN TORSTEN [DE]; KOBLET ANDREAS [CH]; PE) 13 January 2005 (2005-01-13) cited in the application page 4, line 10 - line 13; claims 46-50,52,53	1-36
Y	WO 03/066621 A1 (GLAXO GROUP LTD [GB]; ALVARO GIUSEPPE [IT]; DI FABIO ROMANO [IT]) 14 August 2003 (2003-08-14) page 9, line 16 - line 18; claims 1,12	1-36
Y	WO 03/066635 A (GLAXO GROUP LTD [GB]; ALVARO GIUSEPPE [IT]; DI FABIO ROMANO [IT]; TRAN) 14 August 2003 (2003-08-14) page 14, line 32 - line 34; claim 1	1-36

☐ 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
5 January 2007	18/01/2007

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	MORIGGI, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/008845

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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 claim 35 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the 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

information on patent family members

International application No
PCT/EP2006/008845

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005002577 A	13-01-2005	AU 2004253267 A1	13-01-2005
		BR PI0412291 A	19-09-2006
		CA 2530886 A1	13-01-2005
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		US 2005090533 A1	28-04-2005
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		DE 60302137 T2	20-07-2006
		DK 1472256 T3	20-03-2006
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		IS 7382 A	04-08-2004
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		US 2005176715 A1	11-08-2005
		ZA 200404842 A	26-07-2005

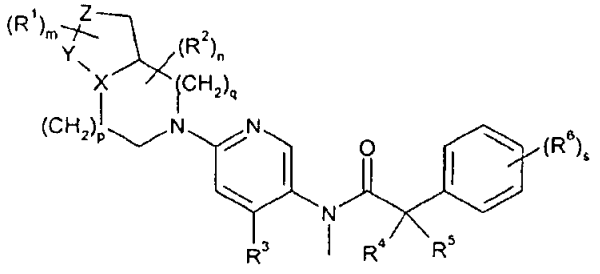
DERIVADOS DE PIRIDINA Y SU USO EN EL TRATAMIENTO DE TRASTORNOS PSICOTICOS

MEMORIA DESCRIPTIVA

La presente invención se refiere a derivados bicíclicos que contienen nitrógeno novedosos que tienen actividad farmacológica, procedimientos para su preparación, a composiciones que los contienen y a su uso en el tratamiento de trastornos psicóticos, en particular esquizofrenia.

El documento WO 2005/002577 (F. Hoffmann-La Roche AG) describe una serie de derivados de piridina que se sostiene que son antagonistas de NK1/NK3 dobles para tratar esquizofrenia.

La presente invención provee, en un primer aspecto, un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo:



(I)

en donde:

X representa un átomo de nitrógeno o azufre;

Y representa $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ o $-C(=O)-$;

Z representa $-C(H_2)-$, $-S(O_2)-$, $-N(R^Z)-$, o un átomo de oxígeno o azufre;

R^z representa hidrógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, $-COR^7$ o $-SO_2R^7$;

R^1 representa halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, =O, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6};

m representa un entero de 0 a 3;

R^2 representa halógeno, =O, alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), $-COOR^7$, $-CONR^7R^8$, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6};

n representa un entero de 0 a 3;

p y q independientemente representan un entero de 0 a 2;

R^3 representa un grupo -arilo, -heteroarilo, -heterociclilo, -aril-arilo, -aril-heteroarilo, -aril-heterociclilo, -heteroaril-arilo, -heteroaril-heteroarilo, -heteroaril-heterociclilo, -heterociclil-arilo, -heterociclil-heteroarilo o -heterociclil-heterociclilo, todos los cuales pueden ser opcionalmente sustituidos por uno o más (v.gr., 1, 2 ó 3) halógeno, grupos alquilo de C_{1-6}, cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, hidroxilo, halogenoalquilo de C_{1-6}, halogenoalcoxi de C_{1-6}, ciano, -S-alquilo de C_{1-6}, -SO-alquilo de C_{1-6}, $-SO_2-$alquilo de C_{1-6}, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, NR^7CO-alquilo de C_{1-6}, NR^7SO_2-alquilo de C_{1-6}, alquilo de C_{1-6}-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ o $-SO_2NR^7R^8$;

R^4 y R^5 independientemente representan alquilo de C_{1-6}, o R^4 y R^5 junto con el átomo de carbono al cual están unidos juntos pueden formar

un grupo cicloalquilo de C_{3-8};

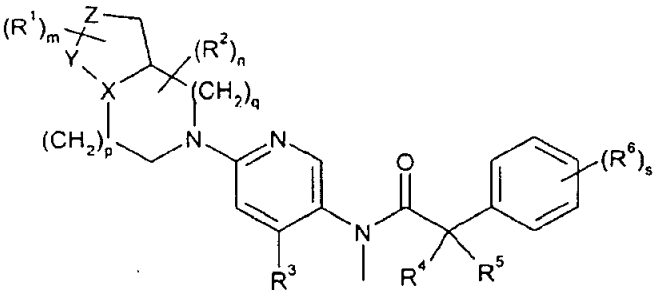
R^6 representa halógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6};

s representa un entero de 0 a 4;

R^7 y R^8 independientemente representan hidrógeno, alquilo de C_{1-6} o cicloalquilo de C_{3-8};

o solvatos de los mismos.

En un aspecto adicional la invención provee un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo:



(I)

en donde:

X representa un átomo de nitrógeno;

Y representa $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ o $-C(=O)-$;

Z representa $-C(H_2)-$, $-S(O_2)-$, $-N(R^Z)-$, o un átomo de oxígeno o azufre;

R^z representa hidrógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, $-COR^7$ o $-SO_2R^7$;

R^1 representa halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, =O,

halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6};

m representa un entero de 0 a 3;

R^2 representa halógeno, =O, alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), $-COOR^7$, $-CONR^7R^8$, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6};

n representa un entero de 0 a 3;

p y q independientemente representan un entero de 0 a 2;

R^3 representa un grupo -arilo, -heteroarilo, -heterociclilo, -aril-arilo, -aril-heteroarilo, -aril- heterociclilo, -heteroaril-arilo, -heteroaril-heteroarilo, -heteroaril-heterociclilo, -heterociclil- arilo, -heterociclil-heteroarilo o -heterociclil-heterociclilo, todos los cuales pueden ser opcionalmente sustituidos por uno o más (v.gr., 1, 2 ó 3) halógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, hidroxilo, halogenoalquilo de C_{1-6}, halogenoalcoxi de C_{1-6}, ciano, -S-alquilo de C_{1-6}, -SO-alquilo de C_{1-6}, $-SO_2$-alquilo de C_{1-6}, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, NR^7CO-alquilo de C_{1-6}, NR^7SO_2-alquilo de C_{1-6}, alquilo de C_{1-6}-NR^7R^8, $-OCONR^7R^8$, $-NR^7CO_2R^8$ o $-SO_2NR^7R^8$;

R^4 y R^5 independientemente representan alquilo de C_{1-6}, o R^4 y R^5 junto con el átomo de carbono al cual están unidos juntos pueden formar un grupo cicloalquilo de C_{3-8};

R^6 representa halógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6};

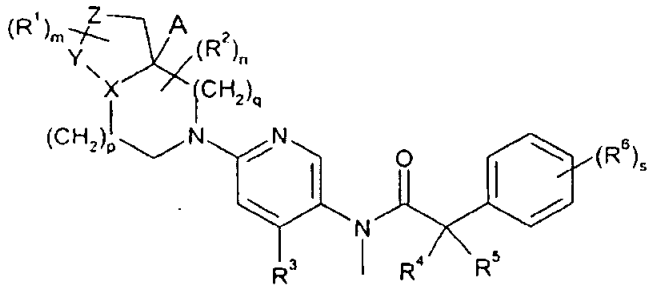
s representa un entero de 0 a 4;

R^7 y R^8 independientemente representan hidrógeno, alquilo de

C_{1-6} o cicloalquilo de C_{3-8};

o solvatos de los mismos.

En otro aspecto, la invención provee un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo:



(I)

en donde:

X representa un átomo de nitrógeno;

Y representa $-C(H_2)-$, $(-C(H_2)-)_2$, $-S(O_2)-$ o $-C(=O)-$;

Z representa $-C(H_2)-$, $-S(O_2)-$, $-N(R^Z)-$, o un átomo de oxígeno o azufre;

A representa hidrógeno o $-CH_2OH$;

R^z representa hidrógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, $-COR^7$ o $-SO_2R^7$;

R^1 representa halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, =O, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6}; hidroxilo o $-CH_2OH$;

m representa un entero de 0 a 3;

R^2 representa halógeno, =O, alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), $-COOR^7$, $-CONR^7R^8$, alcoxi de C_{1-6},

halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6} o alquilo de C_{1-6}-O-alquilo de C_{1-6};

n representa un entero de 0 a 3;

p y q independientemente representan un entero de 0 a 2;

R^3 representa un grupo -arilo, -heteroarilo, -heterociclilo, -aril-arilo, -aril-heteroarilo, -aril- heterociclilo, -heteroaril-arilo, -heteroaril-heteroarilo, -heteroaril-heterociclilo, -heterociclil- arilo, -heterociclil-heteroarilo o -heterociclil-heterociclilo, todos los cuales pueden ser opcionalmente sustituidos por uno o más (v.gr., 1, 2 ó 3) halógeno, alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, hidroxilo, halogenoalquilo de C_{1-6}, halogenoalcoxi de C_{1-6}, ciano, -S-alquilo de C_{1-6}, -SO-alquilo de C_{1-6}, -SO_2-alquilo de C_{1-6}, -COR^7, -$CONR^7R^8$, -NR^7R^8, NR^7CO-alquilo de C_{1-6}, NR^7SO_2-alquilo de C_{1-6}, alquilo de C_{1-6}-NR^7R^8, -$OCONR^7R^8$, -$NR^7CO_2R^8$ o -$SO_2NR^7R^8$;

R^4 y R^5 independientemente representan alquilo de C_{1-6}, o R^4 y R^5 junto con el átomo de carbono al cual están unidos juntos pueden formar un grupo cicloalquilo de C_{3-8};

R^6 representa halógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6};

s representa un entero de 0 a 4;

R^7 y R^8 independientemente representan hidrógeno, alquilo de C_{1-6} o cicloalquilo de C_{3-8};

o solvatos de los mismos.

El término 'alquilo de C_{1-6}' como se usa aquí como un grupo o una parte del grupo se refiere a un grupo hidrocarburo saturado lineal o ramificado que contiene de 1 a 6 átomos de carbono. Ejemplos de dichos grupos incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, ter-butilo, n-pentilo, isopentilo, neopentilo o hexilo y similares.

El término ' alcoxi de C_{1-6}' como se usa aquí se refiere a un -O-alquilo de C_{1-6} en donde alquilo de C_{1-6} es como se define aquí. Ejemplos de dichos grupos incluyen metoxi, etoxi, propoxi, butoxi, pentoxi o hexoxi y similares.

El término 'cicloalquilo de C_{3-8}' como se usa aquí se refiere a un anillo de hidrocarburo monocíclico saturado de 3 a 8 átomos de carbono. Ejemplos de dichos grupos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo o ciclooctilo y similares.

El término 'halógeno' como se usa aquí se refiere a un átomo de flúor, cloro, bromo o yodo.

El término ' halogenoalquilo de C_{1-6}' como se usa aquí se refiere a un grupo alquilo de C_{1-6} como se define aquí en donde por lo menos un átomo de hidrógeno es reemplazado por halógeno. Ejemplos de dichos grupos incluyen fluoroetilo, trifluorometilo o trifluoroetilo y similares.

El término ' halogenoalcoxi de C_{1-6}' como se usa aquí se refiere a un grupo alcoxi de C_{1-6} como se define aquí en donde por lo menos un átomo de hidrógeno es reemplazado por halógeno. Ejemplos de dichos grupos incluyen difluorometoxi o trifluorometoxi y similares.

El término 'arilo' como se usa aquí se refiere a un anillo de hidrocarburo monocíclico o bicíclico de C_{6-12} en donde por lo menos un anillo es aromático. Ejemplos de dichos grupos incluyen fenilo, naftilo o tetrahidronaftalenilo y similares.

El término 'heteroarilo' como se usa aquí se refiere a un anillo aromático monocíclico de 5-6 miembros o un anillo aromático bicíclico de 8-10 miembros que contiene 1 a 4 heteroátomos seleccionados de oxígeno, nitrógeno y azufre. Ejemplos de dichos anillos aromáticos monocíclicos incluyen tienilo, furilo, furazanilo, pirrolilo, triazolilo, tetrazolilo, imidazolilo, oxazolilo, tiazolilo, oxadiazolilo, isotiazolilo, isoxazolilo, tiadiazolilo, piranilo, pirazolilo, pirimidilo, piridazinilo, pirazinilo, piridilo, triazinilo, tetrazinilo y similares. Ejemplos de dichos anillos aromáticos fusionados incluyen quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, pteridinilo, cinolinilo, ftalazinilo, naftiridinilo, indolilo, isoindolilo, azaindolilo, indolizinilo, indazolilo, purinilo, pirrolopiridinilo, furopiridinilo, benzofuranilo, isobenzofuranilo, benzotienilo, benzoimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, benzoxadiazolilo, benzotiadiazolilo y similares.

El término 'heterociclilo' se refiere a un anillo monocíclico de 4-7 miembros o un anillo bicíclico de 8-12 miembros fusionado que puede ser saturado o parcialmente insaturado que contiene 1 a 4 heteroátomos seleccionados de oxígeno, nitrógeno o azufre. Ejemplos de dichos anillos monocíclicos incluyen pirrolidinilo, azetidinilo, pirazolidinilo, oxazolidinilo, piperidinilo, piperazinilo, morpholinilo, tiomorfolinilo, tiazolidinilo, hidantoinilo,

valerolactamilo, oxiranilo, oxetanilo, dioxolanilo, dioxanilo, oxatiolanilo, oxatianilo, ditianilo, dihidrofuranilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, diazepanilo, azepanilo y similares. Ejemplos de dichos anillos bicíclicos incluyen indolinilo, isoindolinilo, benzopiranilo, quinuclidinilo, 2,3,4,5-tetrahidro-1H-3-benzazepina, tetrahidroisoquinolinilo y similares.

En una modalidad, p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa - $C(H_2)$- y Z representa -$C(H_2)$-, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es hexahidropirrolopirazinilo (v.gr., hexahidropirrolo[1,2-a]pirazin-2(1H)-ilo).

En una modalidad alternativa, p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa un átomo de oxígeno, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es hexahidropirazino-oxazinilo (v.gr., hexahidropirazino[2,1-c][1,4]oxazin-8(1H)-ilo).

En una modalidad alternativa adicional, p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -$S(O_2)$- y Z representa -$C(H_2)$-, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es dioxidohexahidroisotiazolopirazinilo (v.gr., 1,1-dioxidohexahidro-5H-isotiazolo[2,3-a]pirazin-5-ilo).

En una modalidad alternativa adicional, p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -C(=O)- y Z representa -$C(H_2)$-, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula

(I) es oxohexahidropirrolopirazinilo (v.gr., 6-oxohexahidropirrolo[1,2-a]pirazin-2(1H)-ilo).

En una modalidad alternativa adicional, p representa 1, q representa 2, X representa un átomo de nitrógeno, Y representa $-C(H_2)-$ y Z representa $-C(H_2)-$, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es octahidropirrolodiazepinilo (v.gr., octahidro-3H-pirrolo[1,2-d][1,4]diazepin-3-ilo).

En una modalidad alternativa adicional, p representa 2, q representa 1, X representa un átomo de nitrógeno, Y representa $-C(H_2)-$ y Z representa $-C(H_2)-$, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es oxahexahidropirrolodiazepinilo (v.gr., oxohexahidro-1H-pirrolo[1,2-a][1,4]diazepin-2(3H)-ilo).

En una modalidad alternativa adicional, p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa $-S(O_2)-$, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es dioxidohexahidropirazinotiazinilo (v.gr., 2,2-dioxidohexahidropirazino[2,1-c][1,4]tiazin-8(1H)-ilo).

En una modalidad adicional, p y q ambos representan 1, X representa nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa $-N(R^Z)-$, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es octahidropirazinopirazinilo (v.gr., octahidro-2H-pirazino[1,2-a]pirazin-2-ilo).

En una modalidad adicional, cuando p representa zero y q representa 1, X representa nitrógeno, Y representa $-C(H_2)-$ y Z representa -

$C(H_2)$-, por ejemplo, la porción bicíclica unida al anillo de piridilo en la fórmula (I) es oxotetrahidropirroloimidazolilo (v.gr., oxotetrahidro-1 H-pirrolo[1,2-c]imidazol-2(3H)-ilo).

En una modalidad, m representa 0.

En otra modalidad, m representa 1.

En una modalidad, cuando m representa 1, R^1 representa =0, hidroxilo, $-CH_2OH$.

En una modalidad, n representa 0 ó 1.

En una modalidad adicional, cuando n representa 1, R^2 representa =0 o alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo; v.gr., $-CH_2-OH$ o CH_3).

En otra modalidad, cuando n representa 1, R^2 representa alquilo de C_{1-6}-O-alquilo de C_{1-6} (v.gr., - CH_2OCH_3) o halogenoalquilo de C_{1-6} (v.gr., - CH_2F).

En otra modalidad más, cuando n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo (v.gr., $-CH_2-OH$).

En una modalidad A representa hidrógeno.

En otra modalidad A representa $-CH_2OH$.

En una modalidad, p y q ambos representan 1 o uno de p o q representa 1 y el otro de p or q representa 2. En una modalidad adicional, p y q ambos representan 1.

En otra modalidad más cuando q representa 1, p representa 0.

En una modalidad, R^7 representa alquilo de C_{1-6} (v.gr., metilo).

En una modalidad, cuando Z representa -N(R^Z)-, R^z representa hidrógeno, alquilo de C_{1-6}, -COR^7 Or -SO_2R^7.

En otra modalidad, R^z representa -COR^7.

En otra modalidad, R^z representa alquilo de C_{1-6} o -SO_2R^7.

En otra modalidad más cuando R^z representa -COR^7, R^7 representa alquilo de C_{1-6} (v.gr., metilo).

En otra modalidad más cuando R^z representa -SO_2R^7, R^7 representa alquilo de C_{1-6} (v.gr., metilo).

En una modalidad, R^3 representa -arilo (v.gr., fenilo) monosustituido por un halógeno (v.gr., 2-cloro) o grupo alquilo de C_{1-6} (v.gr., 2-metilo) o -arilo (v.gr., fenilo) disustituido por un halógeno (v.gr., 4-flúor) y g alquilo de C_{1-6} (v.gr., 2-metilo).

En una modalidad adicional, R^3 representa -arilo (v.gr., fenilo) disustituido por un halógeno (v.gr., 4-flúor) y grupo alquilo de C_{1-6} (v.gr., 2-metilo) (v.gr., 4-fluoro-2-metilfenilo).

En una modalidad adicional R^3 representa -arilo (v.gr., fenilo) monosustituido por alquilo de C_{1-6} sustituido por uno o más grupos hidroxilo (v.gr., -CH_2OH) o -arilo (v.gr., fenilo) disustituido por un halógeno (v.gr., 2-cloro-4-fluorofenilo) o un halógeno (v.gr., 5-flúor) y un grupo alquilo de C_{1-6} (v.gr., 2-metilo) (v.gr., 5-fluoro-2-metilfenilo).

En una modalidad adicional R^3 representa -heteroarilo (v.gr., piridinilo) monosustituido por alquilo de C_{1-6} (v.gr., 6-metilpiridin-3-ilo)) o -heteroarilo (v.gr., piridinilo) disustituido por un halógeno (v.gr., 4-flúor) y un

grupo alquilo de C_{1-6} (v.gr., 2-metilo) (v.gr., 4-fluoro-2-metilpiridin-3-ilo).

En una modalidad, R^4 y R^5 ambos representan alquilo de C_{1-6} (v.gr., metilo), o R^4 y R^5 junto con el átomo de carbono al cual están unidos forman un grupo cicloalquilo de C_{3-8} (v.gr., ciclopropilo). En una modalidad adicional, R^4 y R^5 ambos representan alquilo de C_{1-6} (v.gr., metilo).

En otra modalidad más R^4 y R^5 junto con el átomo de carbono al cual están unidos forman un grupo cicloalquilo de C_{3-8} (v.gr., ciclopropilo).

En una modalidad, s representa 2 y ambos grupos R^6 son halogenoalquilo de C_{1-6} (tal como grupos trifluorometilo, v.gr., 3,5-bis(trifluorometilo)).

En una modalidad, cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa un átomo de oxígeno, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo, R^3 representa -arilo disustituido por un halógeno y grupo alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6} y s representa 2 en donde ambos grupos R^6 son halogenoalquilo de C_{1-6}.

En una modalidad, cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2H_2$ y Z representa $-S(O_2)-$, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo, R^3 representa -arilo disustituido por un halógeno y g alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6} y s representa 2 en donde ambos grupos R^6 son halogenoalquilo de C_{1-6}.

En una modalidad, cuando p y q ambos representan 1, X

representa nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa $-N(R^Z)-$, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo, R^3 representa -arilo disustituido por un halógeno y grupo alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6} y s representa 2 en donde ambos grupos R^6 son halogenoalquilo de C_{1-6}.

En otra modalidad más, p y q ambos representan 1, n y m ambos representan 0, A representa hidrógeno, X representa nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $-N(R^Z)-$, R^3 representa -arilo sustituido por un halógeno y grupo alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6}, s representa 2 en donde ambos grupos R^6 son halogenoalquilo de C_{1-6} y R^z representa - COR_7, en donde R_7 es alquilo de C_{1-6}.

Los compuestos de conformidad con la invención incluyen los ejemplos E1-E33 como se muestra más adelante, o una sal farmacéuticamente aceptable de los mismos.

Los compuestos de conformidad con la invención incluyen los ejemplos E34-E40 como se muestra más adelante, o una sal farmacéuticamente aceptable de los mismos.

Los compuestos de conformidad con la invención incluyen los ejemplos E41-E104 como se muestra más adelante, o una sal farmacéuticamente aceptable de los mismos.

En una modalidad, la invención provee un compuesto seleccionado del grupo que consiste de: 2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S,9aS)-7-(hidroximetil)hexahidropirazino[2,1-

c][1,4]oxazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida,

2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S,9aR)-7-(hidroximetil)hexahidropirazino[2,1-c][1,4]oxazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida,

2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S)-7-(hidroximetilo)-2,2-dioxidohexahidropirazino[2,1-c][1,4]tiazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida,

N-[6-[(3S)-8-acetil-3-(hidroximetilo)octahidro-2H-pirazino[1,2-a]pirazin-2-il]-4-(4-fluoro-2-metilfenilo)-3-piridinil]-2-[3,5-bis(trifluorometilo)fenil]-N,2-dimetilpropanamida, o una sal farmacéuticamente aceptable del mismo.

En una modalidad adicional, la invención provee 2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S,9aR)-7-(hidroximetil)hexahidropirazino[2,1-c][1,4]oxazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida o una sal farmacéuticamente aceptable del mismo.

En una modalidad adicional, la invención provee N-[6-[(9aS o 9aR)-8-acetiloctahidro-2H-pirazino[1,2-a]pirazin-2-il]-4-(4-fluoro-2-metilfenilo)-3-piridinil]-2-[3,5-bis(trifluorometilo)fenil]-N,2-dimetilpropanamida (enantiómero 2) o una sal farmacéuticamente aceptable del mismo, en donde "enantiómero 2" significa un solo enantiómero de estereoquímica absoluta desconocida preparado de conformidad con el ejemplo 72 descrito más adelante.

Los compuestos de la fórmula (I) pueden formar sales ácidas de adición con ácidos, tales como ácidos farmacéuticamente aceptables

convencionales, por ejemplo, maleico, clorhídrico, bromhídrico, fosfórico, acético, fumárico, salicílico, sulfato, cítrico, láctico, mandélico, tartárico y metansulfónico. Sales, solvatos e hidratos de compuestos de la fórmula (I) de los mismos forman un aspecto de la invención.

Como se usa aquí, el término "sal" se refiere a cualquier sal de un compuesto de conformidad con la presente invención preparado a partir de un ácido o base inorgánico u orgánico, sales de amonio cuaternario y sales internamente formadas. Los sales fisiológicamente aceptables son particularmente adecuadas para aplicaciones médicas debido a su mayor solubilidad acuosa en relación con los compuestos progenitores. Dichas sales deben tener claramente un anión o catión fisiológicamente aceptable. Las sales fisiológicamente aceptables adecuadas de los compuestos de la presente invención incluyen sales ácidas de adición formadas con ácidos inorgánicos tales como ácidos clorhídrico, bromhídrico, yodhídrico, fosfórico, metanfosfórico, nítrico y sulfúrico, y con ácidos orgánicos, tales como ácidos tartárico, acético, trifluoroacético, cítrico, málico, láctico, fumárico, benzoico, fórmico, propiónico, glicólico, glucónico, maleico, succínico, alcanforsulfúrico, isotiónico, múcico, gentísico, isonicotínico, sacárico, glucurónico, furoico, glutámico, ascórbico, antranílico, salicílico, fenilacético, mandélico, embónico (pamoico), metansulfónico, etansulfónico, pantoténico, esteárico, sulfinílico, algínico, galacturónico y arilosulfónico, por ejemplo bencensulfónico y p-toluensulfónico; sales básicas de adición formadas con metales alcalinos y metales alcalinotérreos y bases orgánicas tales como N,N-

dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumaina (N-metilglucamina), lisina y procaína; y sales internamente formadas. Las sales que tienen un anión o catión no fisiológicamente aceptable están dentro del alcance de la invención como intermediarios útiles para la preparación de sales fisiológicamente aceptables y/o para usarse en situaciones no terapéuticas, por ejemplo, *in vitro*.

La presente invención también incluye compuestos isotópicamente marcados, que son idénticos a aquellos mencionados en la fórmula (I) y siguientes, excepto por el hecho de que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número atómico diferente de la masa atómica o número atómico usualmente encontrado en la naturaleza. Ejemplos de isótopos que se pueden incorporar en compuestos de la invención y sales farmacéuticamente aceptables de los mismos incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, azufre, flúor, yodo, y cloro, tal como 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O, 31P, 32P, 35S, 18F, 36Cl, 1231 y 1251.

Los compuestos de la presente invención y sales farmacéuticamente aceptables de dichos compuestos que contienen los isótopos antes mencionados y/o otros isótopos de otros átomos están dentro del alcance de la presente invención. Los compuestos isotópicamente marcados de la presente invención, por ejemplo aquellos en los cuales se incorporan isótopos radioactivos tales como 3H, 14C, son útiles en pruebas de distribución de fármaco y/o tejido de sustrato. Isótopos tritiados, es decir, 3H, y

carbono-14, es decir, 14C, son particularmente preferidos para su facilidad de preparación y detección. Los isótopos 11C y 18F son particularmente útiles en PET (tomografía de emisión de positrones), y los isótopos 1251 son particularmente útiles en SPECT (tomografía computarizada de emisión de fotones individuales), todos útiles en formación de imagen del cerebro. Además, la sustitución con isótopos más pesados tales como deuterio, es decir, 2H, pueden dar ciertas ventajas terapéuticas que resultan de mayor estabilidad metabólica, por ejemplo vida media incrementada *in vivo* o requerimientos de dosis reducidos y, por lo tanto, se pueden preferir en algunas circunstancias, Los compuestos isotópicamente marcados de la fórmula I y siguiendo esta invención se pueden preparar generalmente llevando a cabo los procedimientos descritos en los esquemas y/o en los ejemplos que se dan más adelante, utilizando un reactivo isotópicamente marcado fácilmente disponible en vez de un reactivo no isotópicamente marcado.

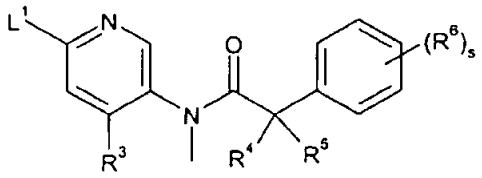
Ciertos compuestos de la fórmula (I) son capaces de existir en formas estereoisoméricas. Se entenderá que la invención abarca todos los isómeros geométricos y ópticos de estos compuestos y las mezclas de los mismos incluyendo racematos. * indica un estereocentro de estereoquímica fija pero desconocida, es decir ya sea estereoquímica R o S. Diastereoisómero 1 o diastereoisómero 2 significa un compuesto de la invención o un intermediario del mismo como un diastereoisómero individual cuya configuración absoluta en un estereocentro no se determinó.

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Enantiómero 1 o enantiómero 2 significa un compuesto de la invención o un intermediario del mismo como un solo enantiómero cuya configuración absoluta no se determinó. Los tautómeros también forman un aspecto de la invención.

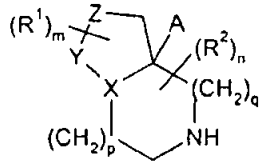
La presente invención también provee un procedimiento para la preparación de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo, dicho procedimiento comprende:

(a) hacer reaccionar un compuesto de la fórmula (II)



(II)

en donde R^3, R^4, R^5, R^6 y s son como se definió antes y L^1 representa un grupo residual adecuado tal como un átomo de halógeno (v.gr., cloro), con un compuesto de la fórmula (III)



(III)

o un derivado opcionalmente protegido del mismo, en donde R^1, R^2, m, n, p, q, X, Y, Z y A son como se definió antes; opcionalmente seguido posteriormente por

(b) desprotección de un compuesto de la fórmula (I) que es

protegido; y

(c) interconversión a otros compuestos de la fórmula (I).

Cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -C(=O)- y Z representa -$C(H_2)$-, el procedimiento (a) se puede realizar en presencia de una base adecuada tal como carbonato de potasio y un solvente adecuado tal como DMSO a una temperatura adecuada, tal como 150-180°C.

Cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-, el procedimiento (a) se puede realizar en presencia de una base adecuada tal como carbonato de potasio y un solvente adecuado tal como DMSO a una temperatura adecuada, tal como 180°C por irradiación de microondas.

Cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo (v.gr., -CH_2-OH), el procedimiento (a) se puede realizar en presencia de una base adecuada tal como terbutóxido de potasio o carbonato de cesio, un solvente adecuado tal como DMSO, un catalizador adecuado tal como bis(dibencilidenacetona)paladio (0.05 eq) un ligando adecuado tal como diciclohexilfosfino-2'-(N,N-dimetilamino)bifenilo (0.125 eq) a una temperatura adecuada, tal como 120°C por irradiación de microondas; o como alternativa, el procedimiento a) se puede realizar en presencia de una base adecuada tal como carbonato de potasio y un solvente adecuado tal como DMSO a una

temperatura adecuada, tal como entre 110 y 160°C.

Alternativamente, cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo (v.gr., -CH_2-OH), el procedimiento (a) se puede realizar sobre el derivado en donde el grupo hidroxilo de R^2 es protegido como un derivado de O-TBDMS, en un solvente adecuado tal como tolueno, en presencia de un catalizador adecuado tal como bis-tri-ter-butilfosfinopaladio, una base adecuada tal como hidróxido de sodio acuoso y un catalizador de transferencia de fase adecuado tal como cloruro de cetiltrimetilamonio acuoso a una temperatura tal como 80-95°C. Este procedimiento puede ser seguido por remoción del grupo protector de TBDMS usando fluoruro de tetrabutilamonio en un solvente adecuado tal como THF, o ácido clorhídrico en un solvente adecuado tal como metanol.

Alternativamente, cuando p y q ambos representan 1, X representa nitrógeno, Y representa -$(C(H_2)$-$)_2$, Z representa un átomo de oxígeno, -$S(O_2)$- o -$N(R^Z)$, n representa 1 y R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo (v.gr., -CH_2-OH) el procedimiento (a) se puede realizar sobre el derivado en donde el grupo hidroxilo de R^2 es protegido como un derivado de O-TBDMS en un solvente adecuado tal como tolueno, en presencia de un catalizador adecuado tal como bis-tri -ter-butilfosfinopaladio, una base adecuada tal como hidróxido de sodio acuoso y un catalizador de transferencia de fase adecuado tal como cloruro de hexadeciltrimetilamonio acuoso a una temperatura tal como 80-95°C. Este

procedimiento puede ser seguido por remoción del grupo protector de TBDMS usando fluoruro de tetrabutilamonio en un solvente adecuado tal como THF, o ácido clorhídrico en un solvente adecuado tal como metanol.

Alternativamente, cuando p y q ambos representan 1, X representa nitrógeno, Y representa $-(C(H_2)-)_2$, Z representa un átomo de oxígeno o $-N(R^Z)$, n representa 1 y R^2 representa alquilo de C_{1-6} o halogenoalquilo de C_{1-6}, el procedimiento (a) se puede realizar en un solvente adecuado tal como tolueno, en presencia de un catalizador adecuado tal como bis-tri -ter-butilfosfinopaladio, una base adecuada tal como hidróxido de sodio acuoso y un catalizador de transferencia de fase adecuado tal como cloruro de hexadeciltrimetilamonio acuoso a una temperatura tal como 80-95°C.

Alternativamente, cuando p y q ambos representan 1, X representa nitrógeno, Y representa $-(C(H_2)-)_2$, Z representa $-N(R^Z)$, n representa 0, m representa 1, y R^1 representa $-CH_2-OH$ el procedimiento (a) se puede realizar en presencia de una base adecuada tal como carbonato de potasio y un solvente adecuado tal como DMSO a una temperatura adecuada, tal como 150°C.

Cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa un átomo de oxígeno o cuando p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $-S(O_2)-$ y Z representa $-C(H_2)-$, o cuando p representa 1, q representa 2, X representa un átomo de nitrógeno, Y representa $-C(H_2)-$ y Z representa $-C(H_2)-$, o cuando p representa 2, q representa 1, X representa un

átomo de nitrógeno, Y representa -C(H_2)-, Z representa -C(H_2)-, n representa 1 y R^2 representa =O, el procedimiento (a) se puede realizar típicamente en presencia de una base adecuada tal como carbonato de potasio, un promotor de reacción adecuado tal como yoduro de cobre en un solvente adecuado tal como DMSO a una temperatura adecuada tal como 150°C por irradiación de microondas.

Cuando p representa 1, q representa 1, X representa un átomo de nitrógeno, Y representa -C(H_2)-, Z representa -C(H_2)-, n representa 1 y R^2 representa =O, el procedimiento (a) se puede realizar típicamente en presencia de N,N'-dimetiletilendiamina, una base adecuada tal como carbonato de cesio, un promotor de reacción adecuado tal como yoduro de cobre en un solvente adecuado tal como dioxano, a una temperatura adecuada tal como 80-120°C.

Cuando p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa (-C(H_2)-)$_2$ y Z representa NH, el procedimiento (a) se puede realizar en presencia de una base adecuada tal como carbonato de potasio y un solvente adecuado tal como DMSO a una temperatura adecuada, tal como 130°C.

En el procedimiento (b), ejemplos de grupos protectores y el medio para su remoción se pueden encontrar en T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Grupos protectores de amina adecuados incluyen sulfonilo (v.gr., tosilo), acilo (v.gr., acetilo, 2',2',2'-tricloroetoxicarbonilo, benciloxicarbonilo o t-butoxicarbonilo) y

ariloalquilo (v.gr., bencilo), que pueden ser removidos por hidrólisis (v.gr., usando un ácido tal como ácido clorhídrico en dioxano o ácido trifluoroacético en diclorometano) o reductivamente (v.gr., hidrogenólisis de un grupo bencilo o remoción reductiva de un grupo 2',2',2'-tricloroetoxicarbonilo usando zinc en ácido acético) según sea apropiado. Otros grupos protectores de amina adecuados incluyen trifluoroacetilo (-$COCF_3$) que pueden ser removidos por hidrólisis catalizada por base o un grupo bencilo unido a resina de fase sólida, tal como un grupo 2,6-dimetoxibencilo unido a resina de Merrifield (enlazador de Ellman), que puede ser removido por hidrólisis catalizada por ácido, por ejemplo con ácido trifluoroacético.

El procedimiento (c) se puede realizar usando procedimientos de interconversión convencionales tales como epimerización, oxidación, reducción, alquilación, substitución aromática nucleofílica o electrofílica, hidrólisis de éster, formación de enlace de amida o reacciones de acoplamiento mediadas por metal de transición. Ejemplos de reacciones de acoplamiento mediadas por metal de transición útiles como procedimientos de interconversión incluyen los siguientes: reacciones de acoplamiento catalizadas por paladio entre electrófilos orgánicos, tales como halogenuros de arilo, y reactivos organometálicos, por ejemplo ácidos borónicos (reacciones de acoplamiento cruzado de Suzuki); reacciones de afinación y amidación catalizadas por paladio entre electrófilos orgánicos, tales como halogenuros de arilo, y nucleófilos, tales como aminas y amidas; reacciones de amidación catalizadas por cobre entre electrófilos orgánicos (tales como

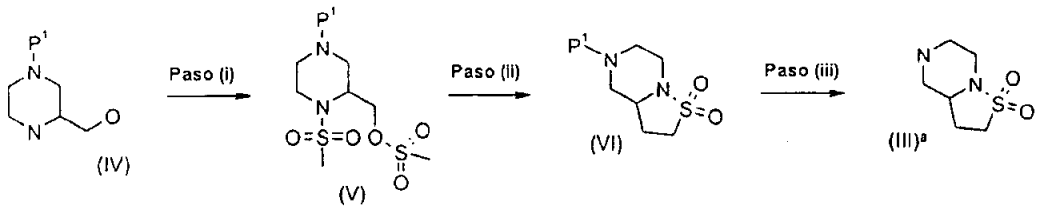
halogenuros de arilo) y nucleófilos tales como amidas; y reacciones de acoplamiento catalizadas por cobre entre fenoles y ácidos borónicos.

Por ejemplo, compuestos de la fórmula (I) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $N(R^Z)$, y R^z representa COR^7 se pueden preparar a partir de compuestos de la fórmula (I) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa NH, mediante acilación usando el cloruro ácido apropiado, en presencia de una base adecuada, tal como trietilamina, en un solvente adecuado, tal como diclorometano. De manera similar, los compuestos de la fórmula (I) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $N(R^Z)$, y R^z representa SO_2R^7 se pueden preparara a partir de compuestos de la fórmula (I) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa NH, mediante sulfonilación usando el cloruro de sulfonilo apropiado en presencia de una base adecuada, tal como trietilamina, en un solvente adecuado, tal como diclorometano. Los compuestos de la fórmula (I) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $N(R^Z)$, y R^z representa alquilo de C_{1-6}, se pueden preparar a partir de compuestos de la fórmula (I) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de

nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa NH, mediante alquilación reductiva utilizando el aldehído apropiado en un solvente adecuado, tal como acetonitrilo, seguido por tratamiento con triacetoxiborohidruro de sodio. Los compuestos de la fórmula (I) en donde p y q ambos representan 1, m representa 0, n representa 1, R^2 representa alquilo de C_{1-6}-O-alquilo de C_{1-6}, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $-S(O)_2-$, se pueden preparar a partir de compuestos de la fórmula (I) en donde p y q ambos representan 1, m representa 0, n representa 1, R^2 representa sustituido por un grupo hidroxilo, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$, y Z representa $-S(O)_2$, mediante alquilación utilizando un halogenuro de alquilo adecuado en presencia de una base, tal como hidruro de sodio, en un solvente adecuado tal como THF.

Los compuestos de la fórmula (II) se pueden preparar de conformidad con la metodología provista en WO 2005/002577.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa $-S(O_2)-$ y Z representa $-C(H_2)-$ se pueden preparar de conformidad con el siguiente esquema:



en donde P^1 representa un grupo protector adecuado tal como

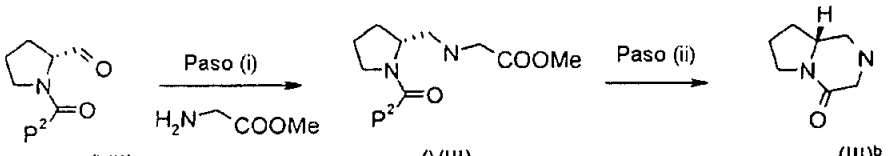
Boc.

El paso (i) típicamente comprende hacer reaccionar un compuesto de la fórmula (IV) con cloruro de metansulfonilo en presencia de un solvente adecuado tal como diclorometano y una base adecuada tal como trietilamina.

El paso (ii) típicamente comprende hacer reaccionar un compuesto de la fórmula (V) con sec-butil-litio en presencia de un solvente adecuado tal como tetrahidrofurano.

El paso (iii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^1 representa Boc dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto de la fórmula (VI) con una mezcla de diclorometano y ácido trifluoroacético.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m representa 0, n representa 1, R^2 representa =0, X representa un átomo de nitrógeno, Y representa $-C(H_2)-$ y Z representa $-C(H_2)-$ se pueden preparar de conformidad con el siguiente esquema:

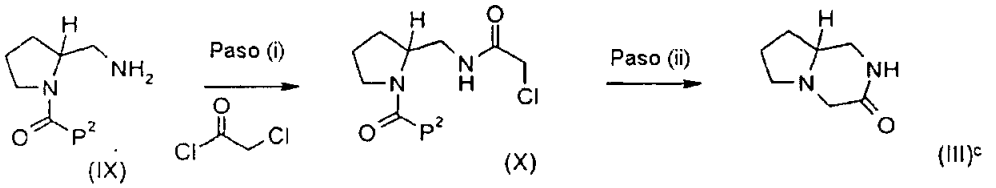


en donde P^2 representa un grupo protector adecuado tal como t-butoxi.

El paso (i) típicamente comprende reacción en presencia de triacetoxiborohidruro de sodio y un ácido adecuado, tal como ácido clorhídrico.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^2 representa t-butoxi dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto de la fórmula (VIII) con una mezcla de diclorometano y ácido trifluoroacético, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte) y calentamiento de las fracciones metabólicas básicas a una temperatura adecuada, tal como 40°C.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m representa 0, n representa 1, R^2 representa =0, X representa un átomo de nitrógeno, Y representa $-C(H_2)-$ y Z representa - $C(H_2)-$ también se pueden preparar de conformidad con el siguiente esquema:



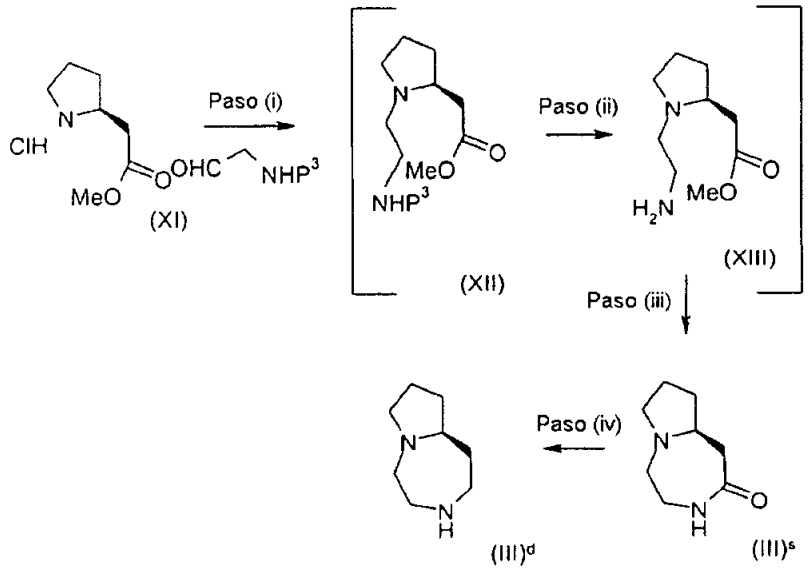
en donde P^2 representa un grupo protector adecuado tal como t-butoxi.

El paso (i) típicamente comprende reacción con cloruro de cloroacetilo en presencia de una base adecuada tal como N,N-diisopropiletilamina en diclorometano.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^2 representa t-butoxi dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto

de la fórmula (X) con una mezcla de diclorometano y ácido trifluoroacético, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte) y calentamiento del intermediario resultante con una base tal como carbonato de sodio en acetonitrilo a una temperatura adecuada, tal como 60°C.

Los compuestos de la fórmula (III) en donde p representa 1, q representa 2, m representa 0, n representa 1, R^2 representa =0, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-, o en donde p representa 1, q representa 2, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$- se pueden preparar de conformidad con el siguiente esquema:



en donde P^3 representa un grupo protector adecuado tal como Boc.

El paso (i) típicamente comprende reacción con (2-

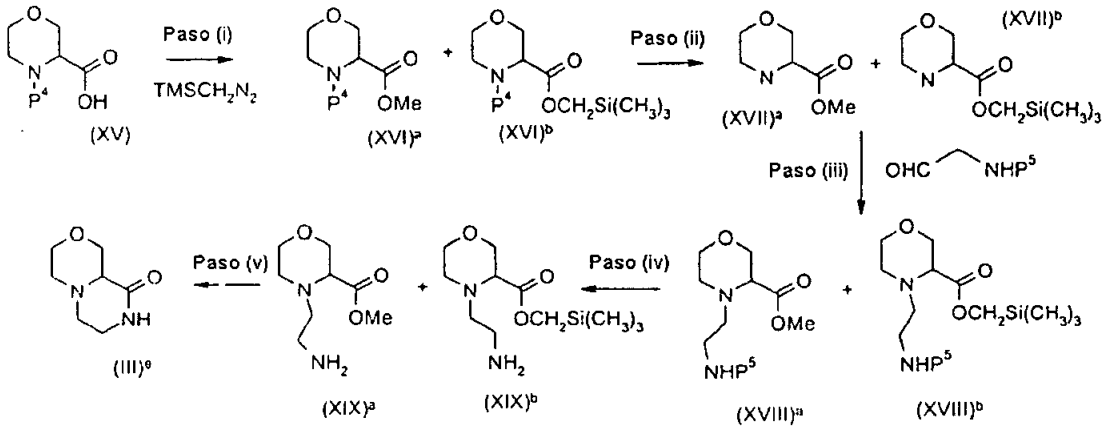
oxoetil)carbamato de 1,1-dimetiletilo en presencia de triacetoxiborohidruro de sodio en un solvente adecuado tal como 1,2-dicloroetano.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^3 representa Boc, dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto de la fórmula (XII) con ácido trifluoroacético en diclorometano, y después purificar el producto sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

El paso (iii) típicamente comprende calentar el intermediario desprotegido previo en un solvente adecuado tal como acetonitrilo a una temperatura adecuada, tal como 60°C.

El paso (iv) típicamente comprende el uso de solución de complejo de borano-tetrahidrofurano a una temperatura adecuada, tal como 0°C, seguido por tratamiento con un ácido acuoso, tal como ácido clorhídrico, y purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m representa O_1 n representa 1, R^2 representa =0, X representa un átomo de nitrógeno, Y representa (-$C(H_2)$-)2 y Z representa un átomo de oxígeno se pueden preparar de conformidad con el siguiente esquema:



en donde P^4 y P^5 representan un grupo protector adecuado tal como Boc.

El paso (i) típicamente comprende hacer reaccionar un compuesto de la fórmula (XV) con una solución de trimetilsililo-diazometano a temperatura ambiente.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^4 representa Boc, dicha reacción de desprotección típicamente puede comprender hacer reaccionar los compuestos de las fórmulas $(XVI)^a$ y $(XVI)^b$ con ácido trifluoroacético en diclorometano.

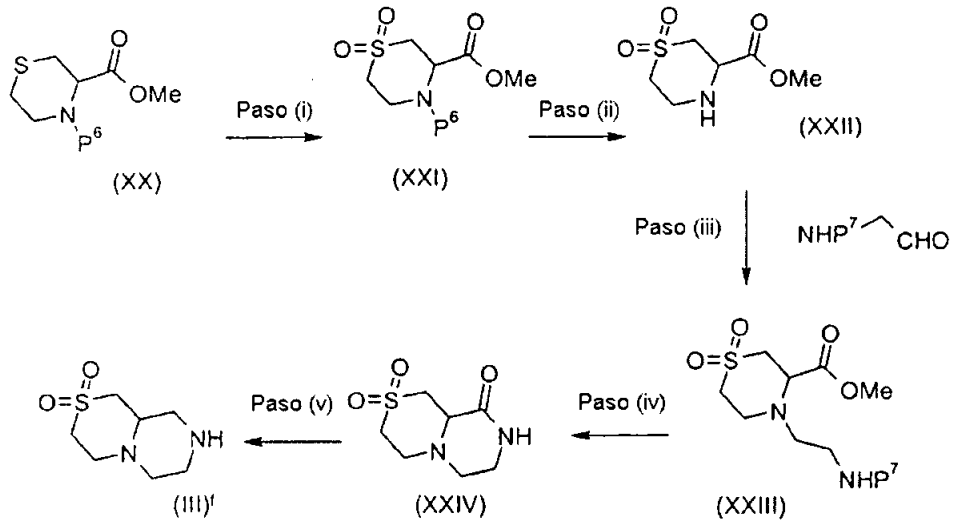
El paso (iii) típicamente comprende hacer reaccionar los compuestos de las fórmulas $(XVM)^a$ y $(XVII)^b$ con N-boc-2-aminoacetaldehído en presencia de triacetoxiborohidruro de sodio en un solvente adecuado tal como 1,2-dicloroetano.

El paso (iv) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^5 representa Boc, dicha reacción de

desprotección típicamente puede comprender hacer reaccionar los compuestos de las fórmulas $(XVIII)^a$ y $(XVIII)^b$ con ácido trifluoroacético en diclorometano, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

El paso (v) típicamente comprende calentar a una temperatura adecuada tal como 40°C los compuestos de las fórmulas $(XIX)^a$ y $(XIX)^b$ en un solvente adecuado tal como metanol.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m y n ambos representan O, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa $-S(O_2)-$ se pueden preparar de conformidad con el siguiente esquema:



en donde P^6 y P^7 representan un grupo protector adecuado tal como Boc.

El paso (i) típicamente comprende hacer reaccionar un compuesto de la fórmula (XX) con MCPBA (ácido 3-cloroperbenzoico) en

diclorometano.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^6 representa Boc, dicha reacción de desprotección típicamente puede comprender hacer reaccionar el compuesto de la fórmula (XXI) con ácido trifluoroacético en diclorometano.

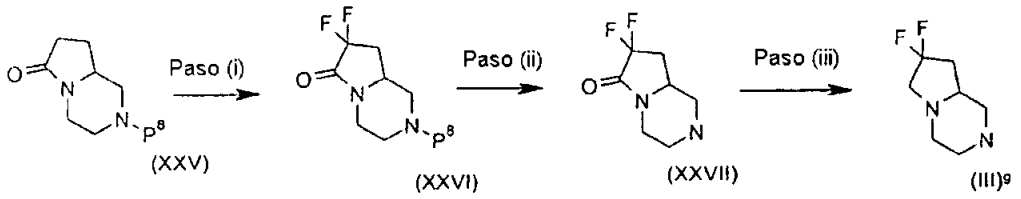
El paso (iii) típicamente comprende hacer reaccionar un compuesto de la fórmula (XXII) con N-boc-2- aminoacetaldehído en presencia de triacetoxiborohidruro de sodio en un solvente adecuado tal como 1,2-dicloroetano.

El paso (iv) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^7 representa Boc, dicha reacción de desprotección típicamente puede comprender hacer reaccionar el compuesto de la fórmula (XXIII) con ácido trifluoroacético en diclorometano seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

El paso (v) típicamente comprende hacer reaccionar un compuesto de la fórmula (XXIV) con solución de complejo de borano-tetrahidrofurano a una temperatura adecuada, tal como 50°C, seguido por tratamiento con un ácido acuoso, tal como ácido clorhídrico, y purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, n representa O, X representa un átomo de nitrógeno, Y representa $-C(H_2)-$, Z representa $-C(H_2)-$, m representa 2 y ambos grupos R^1 representan flúor se pueden preparar de conformidad con el siguiente

esquema:



en donde P^8 representa un grupo protector adecuado tal como t-butoxicarbonilo.

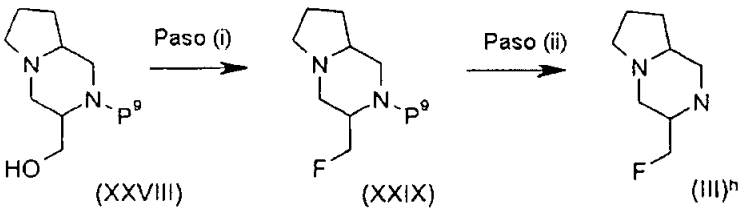
El paso (i) típicamente comprende reacción con una base adecuada tal como bis(dimetiletilsilil)amida de litio en un solvente adecuado tal como THF a una temperatura adecuada tal como -78°C, seguido por un agente de fluoración adecuado tal como N-fluorobencensulfonimida.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^8 representa t-butoxi carbonilo dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto de la fórmula (XXVI) con una mezcla de diclorometano y ácido trifluoroacético, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

El paso (iii) típicamente comprende hacer reaccionar un compuesto de la fórmula (XXVII) con solución de complejo de borano-tetrahidrofurano a una temperatura adecuada, tal como 50°C, seguido por tratamiento con un ácido acuoso, tal como ácido clorhídrico, y purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

Los compuestos de la fórmula (III) en donde p y q ambos

representan 1, m representa 0, X representa un átomo de nitrógeno, Y y Z ambos representan -C(H_2)-, n representa 1 y R^2 representa halogenoalquilo de C_{1-6} (v.gr., fluoroetilo) se pueden preparar de conformidad con el siguiente esquema:



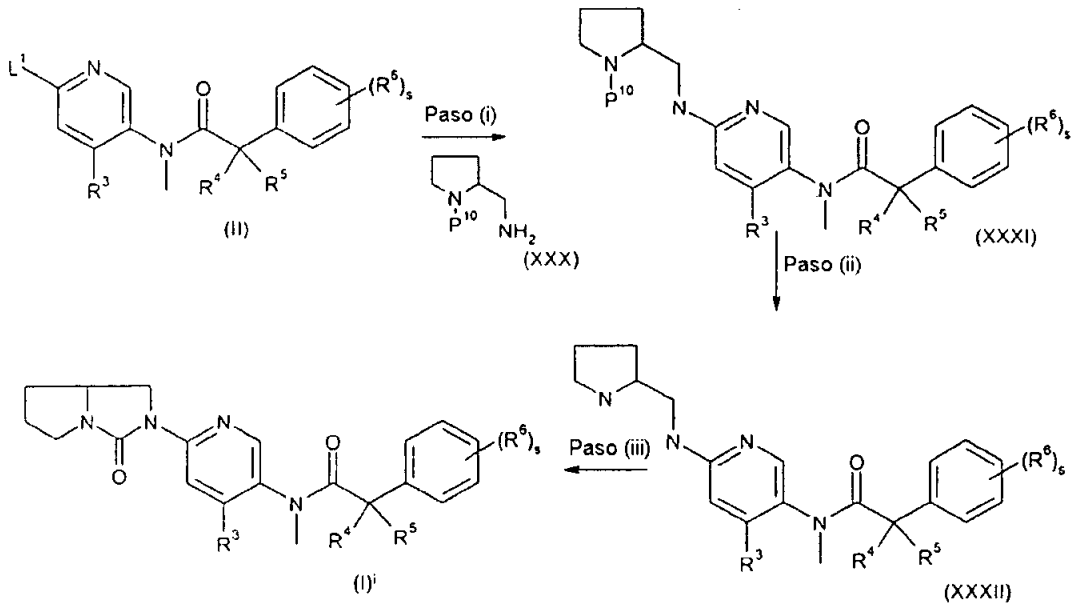
en donde P^9 representa un grupo protector adecuado tal como bencilo.

El paso (i) típicamente comprende reacción con un agente de fluoración tal como DAST (trifluoruro de (dietilamino)azufre) en un solvente adecuado tal como diclorometano a una temperatura adecuada tal como temperatura ambiente.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^9 representa bencilo dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto de la fórmula (XXIX) con hidrógeno en presencia de un catalizador adecuado tal como paladio sobre carbón, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

Los compuestos de la fórmula (I) en donde p representa O_1 q representa 1, m representa 0, n representa 1, R^2 representa =0, X representa un átomo de nitrógeno y Y y Z ambos representan -C(H_2)-, se pueden

preparar de conformidad con el siguiente esquema:



en donde L^1, R^3, R^4, R^5, R^6 y s son como se definió antes y P^{10} representa un grupo residual adecuado tal como Boc.

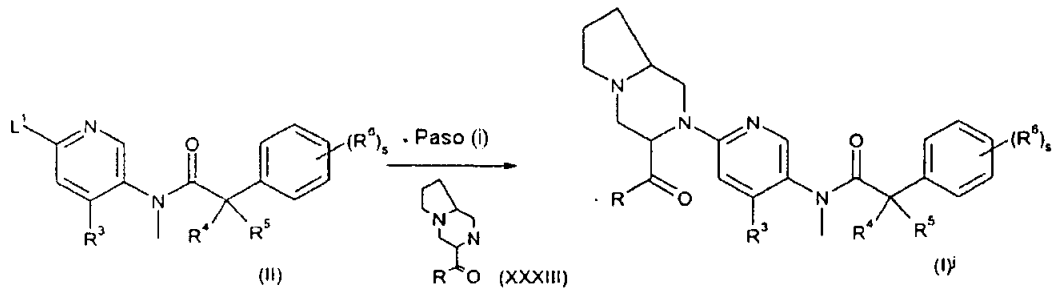
El paso (i) típicamente comprende reacción con 2-(aminometilo)-1-pirrolidincarboxilato de 1,1-dimetiletilo en un solvente adecuado tal como DMSO en presencia de una base adecuada tal como carbonato de potasio a una temperatura adecuada tal como 180°C bajo irradiación de microondas.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^{10} representa Boc dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto de la fórmula (-) con una mezcla de diclorometano y ácido trifluoroacético, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte).

El paso (iii) típicamente comprende hacer reaccionar un

compuesto de la fórmula (XXXI) con trifosgeno en presencia de una base adecuada tal como trietilamina a una temperatura adecuada tal como temperatura ambiente.

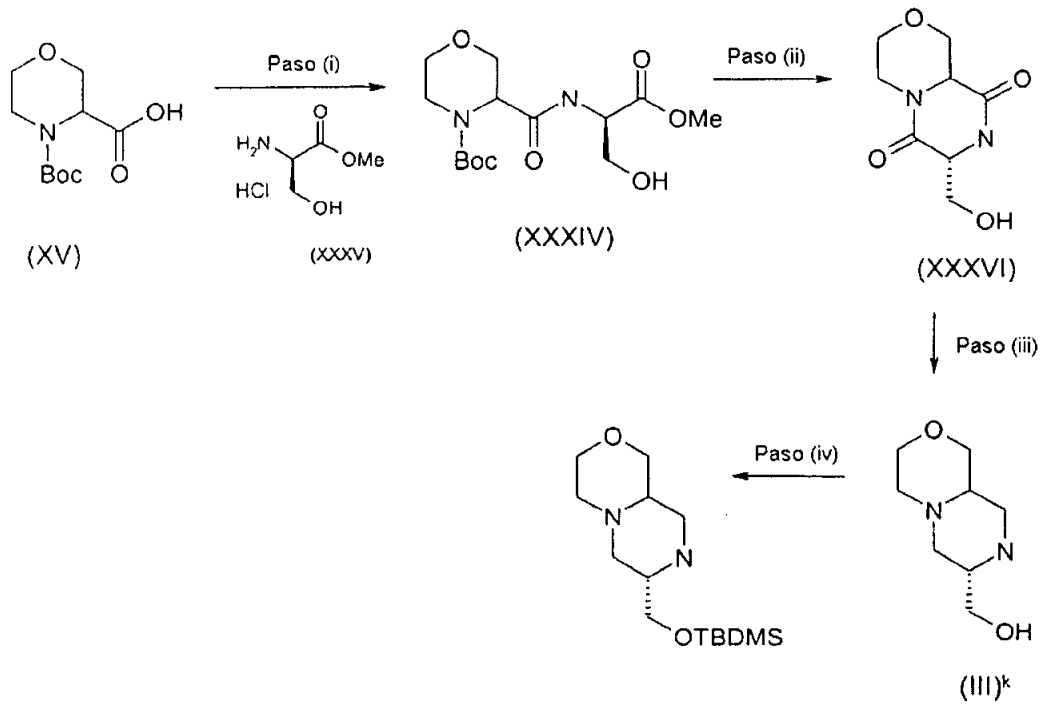
Los compuestos de la fórmula (I) en donde p y q ambos representan 1, m representa 0, n representa 1, R^2 representa -$CONH_2$, CO_2H o CO_2Et, X representa un átomo de nitrógeno y Y y Z ambos representan -$C(H_2)$- se pueden preparar de conformidad con el siguiente esquema:



en donde L^1, R^3, R^4, R^5, R^6 y s son como se definió antes y R representa NH_2, OH o OEt.

El paso (i) típicamente comprende reacción con ácido octahidropirrolo[1,2-a]pirazino-3-carboxílico, amida o éster en presencia de una base adecuada tal como trietilamina a una temperatura adecuada tal como 150°C.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, X representa nitrógeno, Y representa -(C(H_2H_2, Z representa un átomo de oxígeno, m representa 0, n representa 1 y R^2 representa C_{1-6} alquilo sustituido por un grupo hidroxilo, protegido como el derivado de TBDMS, se pueden preparar de conformidad con el siguiente esquema:



El paso (i) típicamente comprende reacción del ácido carboxílico (XV) con la amina de la fórmula (XXXV) en un solvente adecuado, tal como diclorometano, en presencia de un reactivo de acoplamiento adecuado tal como tetrafluoroborato de O-benzotriazol-1-il-N,N,N',N-tetrametiluronio (TBTU) y una base adecuada, tal como diisopropiletilamina a una temperatura adecuada, tal como temperatura ambiente.

El paso (ii) típicamente comprende desprotección de (XXXIV) usando un reactivo adecuado tal como ácido trifluoroacético, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte) y ciclización subsecuente a una temperatura adecuada, tal como 50°C.

El paso (iii) típicamente comprende reducción de (XXXVI) usando un agente reductor adecuado tal como BH_3-THF a una temperatura

adecuada tal como reflujo.

El paso (iv) típicamente comprende reacción de $(III)^k$ con cloruro de ter-butildimetilsililo (TBDMSCl) en un solvente adecuado, tal como diclorometano, en presencia de una base adecuada, tal como trietilamina a una temperatura adecuada, tal como temperatura ambiente.

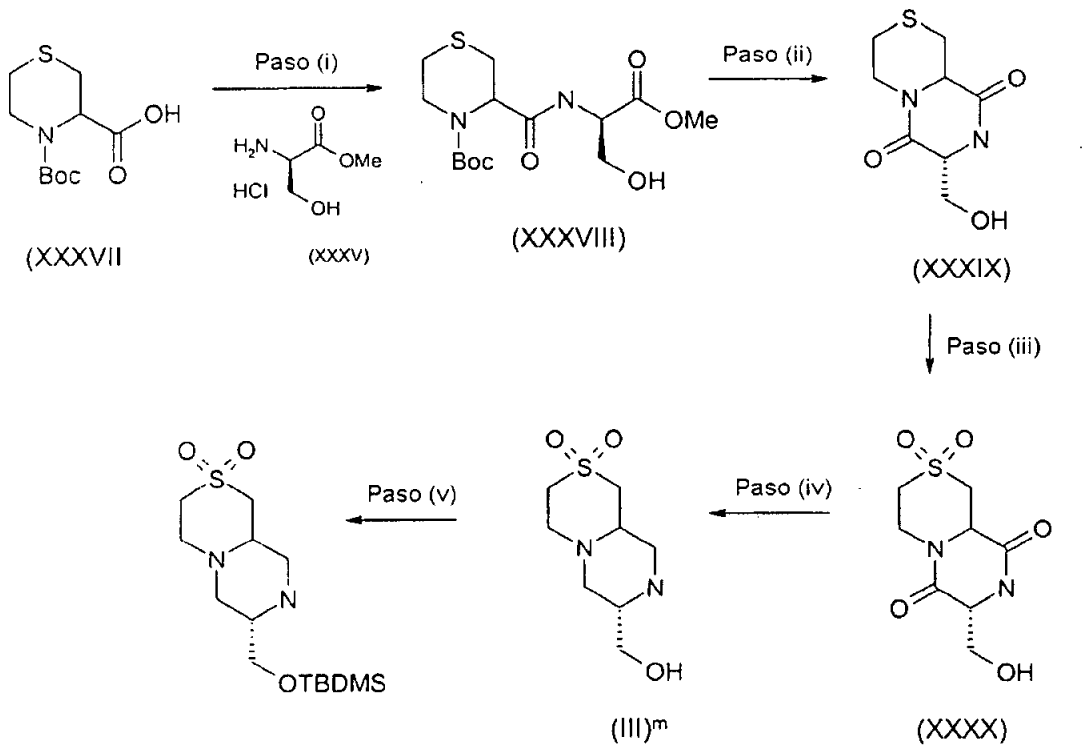
Los compuestos de la fórmula (III) en donde p y q ambos representan 1, X representa nitrógeno, Y representa $-(C(H_2)-)_2$, Z representa un átomo de oxígeno, m representa 0, n representa 1 y R^2 representa C_{1-6} alquilo se pueden preparar de una manera análoga a la descrita anteriormente, empezando a partir de la amina apropiada en lugar del de la fórmula (XXXV) anterior.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, X representa nitrógeno, Y representa $-(C(H_2H_2$, Z representa $-N(R^Z)-$, m representa 0, n representa 1 y R^2 representa C_{1-6} alquilo sustituido por un grupo hidroxilo, protegido como el derivado de TBDMS, se pueden preparar de una manera análoga a la descrita anteriormente cuando Z representa un átomo de oxígeno, empezando a partir del ácido carboxílico correspondiente en donde Z representa $N-P^{11}$ y P^{11} representa un grupo protector adecuado tal como Boc. Los compuestos de la fórmula (III) en donde R^z es alquilo de C_{1-6}, alcoxi de C_{1-6}, $-COR^7$ o $-SO_2R^7$ se pueden derivar de los compuestos de la fórmula (III) cuando R^z es hidrógeno en cualquier punto en la secuencia sintética, por ejemplo después del paso (iv), mediante desprotonación utilizando una base adecuada tal como trietilamina seguida

por reacción del anión resultante con R^z-L^2, en donde L^2 es un grupo residual adecuado tal como halógeno, bajo condiciones estándares, descritas en muchos textos de química orgánica estándares, tales como 'March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure[1] de Michael B. Smith y Jerry March, quinta edición (Wiley, 2001), incorporada aquí por referencia.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, X representa nitrógeno, Y representa $-(C(H_2)-)_2$, Z representa $-N(R^Z)-$, m representa 0, n representa 1 y R^2 representa alquilo de C_{1-6}, se pueden preparar de una manera análoga a la descrita anteriormente cuando Z representa un átomo de oxígeno, empezando a partir del ácido carboxílico correspondiente, en donde Z representa N-P^{11} y P^{11} representan un grupo protector adecuado tal como Boc, y la amina apropiada en lugar de la de la fórmula (XXXV) anterior. Los compuestos de la fórmula (III) en donde R^z es alquilo de C_{1-6}, alcoxi de C_{1-6}, $-COR^7$ o $-SO_2R^7$ se pueden derivar de los compuestos de la fórmula (III) cuando R^z es hidrógeno en cualquier punto en la secuencia sintética mediante la desprotonación utilizando una base adecuada tal como trietilamina seguida por reacción del anión resultante con R^z-L^2, en donde L^2 es un grupo residual adecuado tal como halógeno, bajo condiciones estándares, descrito en cualesquiera de muchos textos de química orgánica estándares, tales como 'March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure' de Michael B. Smith y Jerry March, quinta edición (Wiley, 2001), incorporada aquí por referencia.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, X representa nitrógeno, Y representa -(C(H_2H_2, Z representa -$S(O_2)$-, n representa 1 y R^2 representa C_{1-6} alquilo sustituido por un grupo hidroxilo, protegido como el derivado de TBDMS, se pueden preparar de conformidad con el siguiente esquema:



El paso (i) típicamente comprende reacción del ácido carboxílico (XXXVII) con la amina de la fórmula (XXXV) en un solvente adecuado, tal como diclorometano, en presencia de un reactivo de acoplamiento adecuado tal como tetrafluoroborato de O-benzotriazol-1-il-N,N,N',N'-tetrametiluronio (TBTU) y una base adecuada, tal como diisopropiletilamina a una temperatura adecuada, tal como temperatura ambiente.

El paso (ii) típicamente comprende desprotección de (XXXVIII)

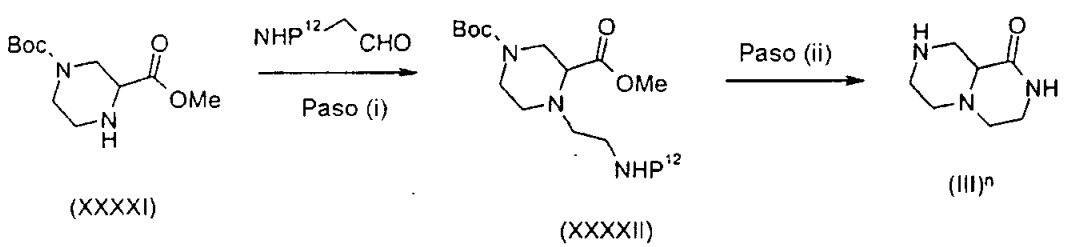
usando un reactivo adecuado tal como ácido trifluoroacético, seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte) y ciclización subsecuente bajo condiciones estables, tales como irradiación de microondas.

El paso (iii) típicamente comprende oxidación de (XXXIX) utilizando un agente oxidante adecuado tal como ácido 3-cloroperoxibenzoico (m-CPBA), en un solvente adecuado tal como diclorometano, a una temperatura adecuada, tal como temperatura ambiente.

El paso (iv) típicamente comprende reducción de (XXXX) usando un agente reductor adecuado tal como BH_3-THF a una temperatura adecuada tal como reflujo.

El paso (v) típicamente comprende reacción de $(III)^m$ con cloruro de ter-butildimetilsililo (TBDMSCl) en un solvente adecuado, tal como diclorormetano, en presencia de una base adecuada, tal como trietilamina a una temperatura adecuada, tal como temperatura ambiente.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m representa 0, n representa 1, R^2 representa =0, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa NH se pueden preparar de conformidad con el siguiente esquema:



(XXXXI) (XXXXII) $(III)^n$

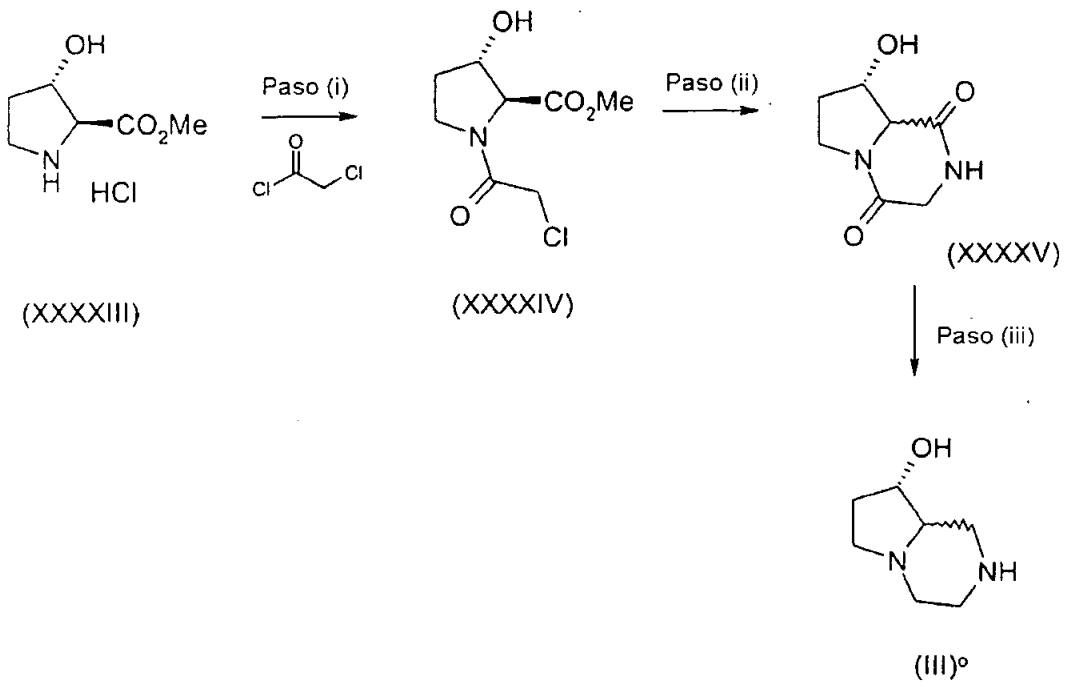
en donde P^{12} representa un grupo protector adecuado tal como Boc.

El paso (i) típicamente comprende hacer reaccionar un compuesto de la fórmula (XXXXI) con N-boc-2-aminoacetaldehído en presencia de triacetoxiborohidruro de sodio en un solvente adecuado tal como 1,2-dicloroetano.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P^{12} representa Boc, dicha reacción de desprotección típicamente puede comprender hacer reaccionar el compuesto de la fórmula (XXXXII) con ácido trifluoroacético en diclorometano seguido por purificación sobre un cartucho de sílice SCX (intercambio catiónico fuerte), seguido por ciclización.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m y n ambos representan 0, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa NH se pueden preparar a partir de compuestos de la fórmula $(III)^n$ mediante reducción con un agente reductor adecuado tal como borano-THF, a temperatura elevada, tal como 75°C, en un solvente adecuado, tal como THF.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m representa 1, n representa 0, R^1 representa hidroxilo, X representa un átomo de nitrógeno, Y representa $-C(H_2)$ y Z representa $-C(H_2)$ se pueden preparar de conformidad con el siguiente esquema:



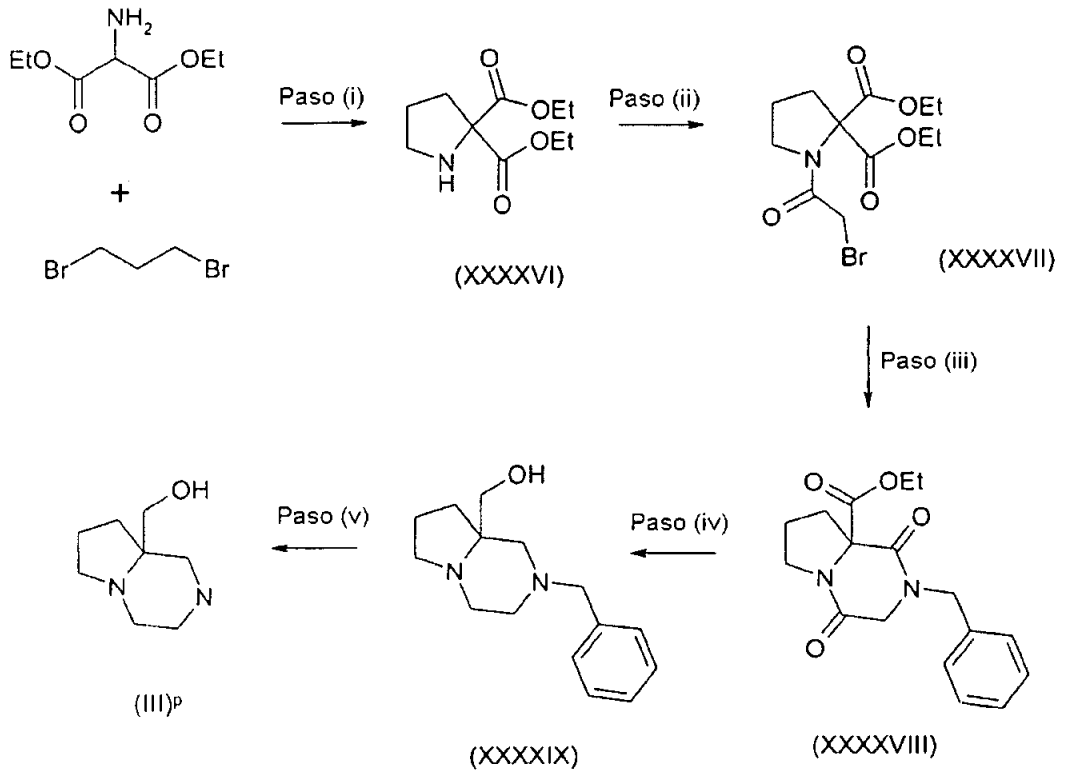
(XXXXIII) (XXXXIV) (III)°

El paso (i) típicamente comprende hacer reaccionar un compuesto de la fórmula (XXXXIII) con cloruro de cloroacetilo en presencia de una base adecuada, tal como trietilamina.

El paso (ii) típicamente comprende tratar (XXXXIV) con amoniaco metanólico a temperatura ambiente.

El paso (iii) típicamente comprende reducción de la dicetopiperazina de la fórmula (XXXXV) con un agente reductor adecuado, tal como $LiAlH_4$, en un solvente adecuado, tal como THF, a temperatura ambiente.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m y n ambos representan O, X representa un átomo de nitrógeno, Y representa -$C(H_2)$, Z representa -$C(H_2)$ y A representa CH_2OH se pueden preparar de conformidad con el siguiente esquema:



Típicamente, los compuestos de la fórmula (XXXXVI) se pueden preparar haciendo reaccionar aminomalonato de dietilo con 1,3-dibromopropano en presencia de etóxido de sodio, en un solvente adecuado tal como etanol, a una temperatura elevada adecuada, tal como reflujo (paso (i)).

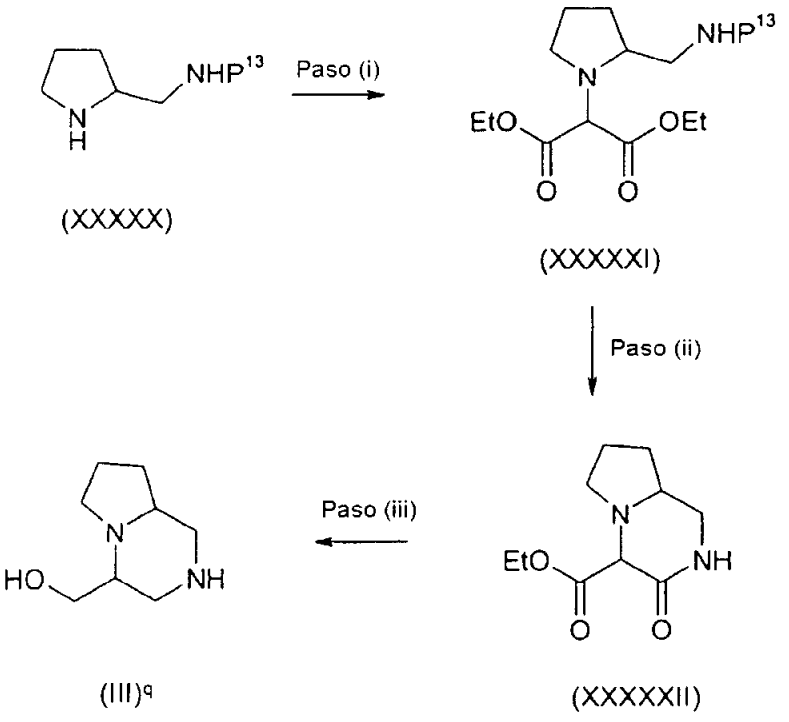
El paso típico (ii) se puede realizar mediante reacción de (XXXXVI) con bromuro de bromoacetilo en presencia de una base adecuada, tal como carbonato de potasio a 0°C.

El paso típico (iii) implica tratamiento de (XXXXVII) con bencilamina en un solvente adecuado, tal como acetonitrilo, a temperatura ambiente.

El paso típico (iv) implica reducción de (XXXXVIII) usando un agente reductor adecuado tal como $LiAlH_4$, en un solvente adecuado tal como THF a temperatura elevada, tal como reflujo.

El paso típico (v) implica desprotección bajo condiciones estándares, tal como tratar con formiato de amonio y paladio sobre carbón, en un solvente adecuado tal como metanol, a una temperatura elevada, tal como reflujo.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, m representa O, n representa 1, R^2 representa CH_2OH, X representa un átomo de nitrógeno, Y representa $-C(H_2)$, Z representa $-C(H_2)$ se pueden preparar de conformidad con el siguiente esquema:



en donde P^{13} representa un grupo protector adecuado tal como

benciloxicarbonilo.

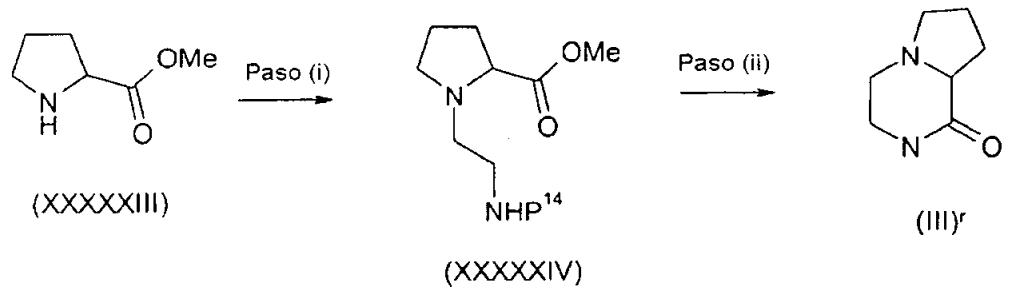
El paso típico (i) se puede realizar por reacción de un compuesto de la fórmula (XXXXX) con bromomalonato de dietilo en presencia de una base, tal como carbonato de potasio, en un solvente adecuado, tal como acetonitrilo a temperatura ambiente.

El paso típico (ii) se puede realizar mediante desprotección de compuesto (XXXXXI) bajo condiciones estándares, tal como bajo una atmósfera de hidrógeno en presencia de paladio sobre carbón, seguido por ciclización a una temperatura elevada, tal como 50°C.

El paso típico (iii) se puede realizar mediante reducción de la porción éster de (XXXXXII) utilizando el un agente reductor adecuado, tal como $LiBH_4$ en un solvente tal como THF, seguido por reducción de la porción carbonilo de la amida utilizando un reactivo adecuado, tal como BH_3-THF, una temperatura elevada, tal como reflujo.

Los compuestos de la fórmula (III) en donde p y q ambos representan 1, X representa nitrógeno, Y representa -(C(H_2H_2, Z representa un átomo de oxígeno, m representa 0, n representa 1 y R^2 representa halogenoalquilo de C_{1-6} se pueden preparar a partir de compuestos de la fórmula $(III)^k$ mediante protección del NH secundario, por ejemplo usando un grupo bencilo, seguido por conversión de la porción hidroxialquilo a una porción halogenoalquilo de C_{1-6} mediante tratamiento con un agente halogenante tal como DAST [trifluoruro de (dietilamino)azufre], seguido por desprotección bajo condiciones estándares.

Los compuestos de la fórmula (III) en donde p representa 1, q representa 1, m representa O_1 n representa 1, R^2 representa =O, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$- se pueden preparar de conformidad con el siguiente esquema:



(XXXXXIII) (XXXXXIV) $(III)^r$

en donde P^{14} representa un grupo protector adecuado tal como Boc.

El paso típico (i) se puede realizar mediante reacción de (XXXXXIII) con (2-oxoetilo)carbamato de 1,1-dimetiletilo en presencia de triacetoxiborohidruro de sodio en un solvente adecuado tal como 1,2-dicloroetano.

El paso (ii) típicamente comprende una reacción de desprotección, por ejemplo, cuando P representa Boc, dicha reacción de desprotección típicamente puede comprender hacer reaccionar un compuesto de la fórmula (XXXXXIV) con ácido trifluoroacético en diclorometano, y después purificar el producto sobre un cartucho de sílice SCX (intercambio catiónico fuerte). El intermediario desprotegido se puede ciclizar calentando a una temperatura adecuada, tal como 40°C.

Los compuestos de la fórmula (IV), (VII), (IX), (XI), (XV), (XX),

(XXV), (XXVIII), (XXX), (XXXIII), (XXXV), (XXXVII).(XXXXI), (XXXXIII), (XXXXX) y (XXXXXIII) son ya sea conocidos o se pueden preparar de conformidad con procedimientos conocidos. 760

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables tienen afinidad y son antagonistas del receptor de NK1 y NK3 y por lo tanto se pueden usar en el tratamiento de trastornos psicóticos.

Dentro del contexto de la presente invención, los términos que describen las indicaciones usadas aquí se clasifican en Diagnostic and Statistical Manual of Mental Disorders, 4ª. edición, publicado por la American Psychiatric Association (DSM-IV) y/o the International Classification of Diseases, 10ª. edición (ICD-10). Los diversos tipos de los trastornos mencionados aquí se contemplan como parte de la presente invención. Los números entre corchetes después de las enfermedades listadas a continuación se refieren al código de clasificación en DSM-IV.

Dentro del contexto de la presente invención, el término "trastorno psicótico" incluye: - esquizofrenia incluyendo los subtipos de tipo paranoide (295.30), tipo desorganizado (295.10), tipo catatónico (295.20), tipo indiferenciado (295.90) y tipo residual (295.60); trastorno esquizofrénico (295.40); trastorno esquizoafectivo (295.70) incluyendo los subtipos de tipo bipolar y tipo depresivo; trastorno de delirio (297.1) incluyendo los subtipos de tipo erotomaniaco, tipo grandioso, tipo celoso, tipo persecución, tipo somático, tipo mixto y tipo no especificado; trastorno psicótico breve (298.8); trastorno psicótico compartido (297.3); trastorno psicótico debido a una condición

médica general incluyendo los subtipos con delirios y con alucinaciones; trastorno psicótico inducido por sustancias incluyendo los subtipos con delirios (293.81) y con alucinaciones (293.82); y trastornos psicóticos de otra manera no especificados (298.9).

Los compuestos de la fórmula (I) y sales y solvatos farmacéuticamente aceptables de los mismos también se pueden usar en el tratamiento de los siguientes trastornos:-

Depresión y trastornos del estado de ánimo incluyendo episodio depresivo mayor, episodio maniaco, episodio mixto y episodio hipomaniaco; trastornos depresivos incluyendo trastorno depresivo mayor, trastorno distímico (300.4), trastorno depresivo de otra manera no especificado (311); trastornos bipolares incluyendo trastorno bipolar I, trastorno bipolar II (episodios depresivos mayores recurrentes con episodios hipomaniacos) (296.89), trastorno ciclotímico (301.13) y trastorno bipolar de otra manera no especificado (296.80); otros trastornos del estado de ánimo incluyendo trastorno del estado de ánimo debido a una condición médica general (293.83) que incluye los subtipos con características depresivas, con episodio similar al depresivo mayor, con características maniacas y con características mixtas), trastorno del estado de ánimo inducido por sustancias (incluyendo los subtipos con características depresivas, con características maniacas y con características mixtas) y trastorno del estado de ánimo de otra manera no especificado (296.90):

Los trastornos de ansiedad incluyendo ataque de pánico;

trastorno de pánico incluyendo trastorno de pánico sin agorafobia (300.01) y trastorno de pánico con agorafobia (300.21); agorafobia; agorafobia sin historia de trastorno de pánico (300.22), fobia específica (300.29, anteriormente fobia simple) incluyendo los subtipos de tipo animal, tipo de ambiente natural, tipo de sangre-inyección-lesión, tipo situacional y otro tipo), fobia social (trastorno de ansiedad social, 300.23), trastorno obsesivo-compulsivo (300.3), trastorno de estrés post-traumático (309.81), trastorno de estrés agudo (308.3), trastorno de ansiedad generalizada (300.02), trastorno de ansiedad debida a una condición médica general (293.84), trastorno de ansiedad inducido por sustancias, trastorno de ansiedad por separación (309.21), trastornos de ajuste con ansiedad (309.24) y trastorno de ansiedad de otra manera no especificado (300.00):

Trastornos relacionados con sustancias incluyendo trastornos de usos de sustancias tales como dependencia de sustancias, Anhelo de sustancias y abuso de sustancias; trastornos inducidos por sustancias tales como intoxicación por sustancias, abstinencia a sustancias, delirio inducido por sustancias, demencia persistente inducida por sustancias, trastorno amnésico persistente inducido por sustancias, trastorno psicótico inducido por sustancias, trastorno del estado de ánimo inducido por sustancias, trastorno de ansiedad inducido por sustancias, disfunción sexual inducida por sustancias, trastorno del sueño inducido por sustancias y trastorno de percepción persistente alucinógeno (retrospección); trastornos relacionados con alcohol tales como dependencia del alcohol (303.90), abuso del alcohol

(305.00), intoxicación por alcohol (303.00), abstinencia al alcohol (291.81), delirio por intoxicación con alcohol, delirio por abstinencia al alcohol, demencia persistente inducida por alcohol, trastorno amnésico persistente inducido por alcohol, trastorno psicótico inducido por alcohol, trastorno del estado de ánimo inducido por alcohol, trastorno de ansiedad inducido por alcohol, disfunción sexual inducida por alcohol, trastorno del sueño inducido por alcohol y trastorno relacionado con alcohol de otra manera no especificado (291.9); trastornos relacionados con anfetaminas (o similares a anfetaminas) tales como dependencia de anfetaminas (304.40), abuso de anfetaminas (305.70), intoxicación por anfetaminas (292.89), abstinencia a anfetaminas (292.0), delirio por intoxicación con anfetaminas, trastorno psicótico inducido por anfetaminas, trastorno del estado de ánimo inducido por anfetaminas, trastorno de ansiedad inducido por anfetaminas, disfunción sexual inducida por anfetaminas, trastorno del sueño inducido por anfetaminas y trastorno relacionado con anfetaminas de otra manera no especificado (292.9); trastornos relacionados con cafeína tales como intoxicación por cafeína (305.90), trastorno de ansiedad inducido por cafeína, trastorno del sueño inducido por cafeína y trastorno relacionado con cafeína de otra manera no especificado (292.9); trastornos relacionados con *Cannabis* tales como dependencia de *Cannabis* (304.30), abuso de *Cannabis* (305.20), intoxicación por *Cannabis* (292.89), delirio por intoxicación con *Cannabis*, trastorno psicótico inducido por *Cannabis*, trastorno de ansiedad inducido por *Cannabis* y trastorno relacionado con *Cannabis* de otra manera no especificado (292.9);

trastornos relacionados con cocaína tales como dependencia de cocaína (304.20), abuso de cocaína (305.60), intoxicación por cocaína (292.89), abstinencia a cocaína (292.0), delirio por intoxicación con cocaína, trastorno psicótico inducido por cocaína, trastorno del estado de ánimo inducido por cocaína, trastorno de ansiedad inducido por cocaína, disfunción sexual inducida por cocaína, trastorno del sueño inducido por cocaína y trastorno relacionado con cocaína de otra manera no especificado (292.9); trastornos relacionados con alucinógenos tales como dependencia de alucinógenos (304.50), abuso de alucinógenos (305.30), intoxicación por alucinógenos (292.89), trastorno de percepción persistente de alucinógenos (retrospección) (292.89), delirio por intoxicación con alucinógenos, trastorno psicótico inducido por alucinógenos, trastorno del estado de ánimo inducido por alucinógenos, trastorno de ansiedad inducido por alucinógenos y trastorno relacionado con alucinógenos de otra manera no especificado (292.9); trastornos relacionados con inhalantes tales como dependencia de inhalantes (304.60), abuso de inhalantes (305.90), intoxicación por inhalantes (292.89), delirio por intoxicación con inhalantes, demencia persistente inducida por inhalantes, trastorno psicótico inducido por inhalantes, trastorno del estado de ánimo inducido por inhalantes, trastorno de ansiedad inducido por inhalantes y trastorno relacionado con inhalantes de otra manera no especificado (292.9); trastornos relacionados con nicotina tales como dependencia de nicotina (305.1), abuso de nicotina (292.0) y trastorno relacionado con nicotina de otra manera no especificado (292.9); trastornos relacionados con opioides tales

como dependencia de opioides (304.00), abuso de opioides (305.50), intoxicación por opioides (292.89), abstinencia a opioides (292.0), delirio por intoxicación con opioides, trastorno psicótico inducido por opioides, trastorno del estado de ánimo inducido por opioides, disfunción sexual inducida por opioides, trastorno del sueño inducido por opioides y trastorno relacionado con opioides de otra manera no especificado (292.9); trastornos relacionados con fenciclidina (o similar a fenciclidina) tales como dependencia de fenciclidina (304.60), abuso de fenciclidina (305.90), intoxicación por fenciclidina (292.89), delirio por intoxicación con fenciclidina, trastorno psicótico inducido por fenciclidina, trastorno del estado de ánimo inducido por fenciclidina, trastorno de ansiedad inducido por fenciclidina y trastorno relacionado con fenciclidina de otra manera no especificado (292.9); trastornos relacionados con sedantes, hipnóticos o ansiolíticos tales como sedantes, dependencia de hipnóticos o ansiolíticos (304.10), abuso de sedantes, hipnóticos o ansiolíticos (305.40), intoxicación por sedantes, hipnóticos o ansiolíticos (292.89), abstinencia a sedantes, hipnóticos o ansiolíticos (292.0), delirio por intoxicación co sedantes, hipnóticos o ansiolíticos, delirio por abstinencia a sedantes, hipnóticos o ansiolíticos, demencia persistencia por sedantes, hipnóticos o ansiolíticos, trastorno amnésico persistente por sedantes, hipnóticos o ansiolíticos, trastorno psicótico inducido por sedantes, hipnóticos o ansiolíticos, trastorno del estado de ánimo inducido por sedantes, hipnóticos o ansiolíticos, trastorno de ansiedad inducido por sedantes, hipnóticos o ansiolíticos, disfunción sexual inducida por sedantes, hipnóticos o ansiolíticos,

trastorno del sueño inducido por sedantes, hipnóticos o ansiolíticos y trastorno relacionado con sedantes, hipnóticos o ansiolíticos de otra manera no especificado (292.9); trastornos relacionados con polisustancias tales como dependencia de polisustancias (304.80); y otros trastornos relacionados con sustancias (o desconocidos) tales como esteroides anabólicos, inhalantes de nitrato y óxido nítrico:

Los trastornos del sueño incluyendo trastornos del sueño primarios tales como Disomnias tal como insomnio primario (307.42), hipersomnio primario (307.44), narcolepsia (347), trastornos del sueño relacionados con la respiración (780.59), trastornos del sueño relacionados con el ritmo circadiano (307.45) y Disomnia de otra manera no especificado (307.47); trastornos del sueño primarios tal como Parasomnias tal como trastorno de pesadillas (307.47), trastornos de terror en los sueños (307.46), trastorno de sonambulismo (307.46) y Parasomnia de otra manera no especificado (307.47); trastornos del sueño relacionados con otro trastorno mental tal como insomnio relacionado con otro trastorno mental (307.42) e hipersomnia relacionada con otro trastorno mental (307.44); trastorno del sueño debido a condición médica general, en particular perturbaciones del sueño asociadas con enfermedades tales como trastornos neurológicos, dolor neuropático, síndrome de piernas sin descanso, enfermedades cardiacas y pulmonares; y trastorno del sueño inducido por sustancias incluyendo los subtipos de tipo de insomnio, tipo de hipersomnia, tipo de parasomnia y tipo mixto; apnea de sueño y síndrome de desarreglo psicofísico:

Trastornos de la alimentación tales como anorexia nerviosa (307.1) incluyendo los subtipos de tipo restrictivo y tipo atracón/purga; bulimia nerviosa (307.51) incluyendo los subtipos de tipo purga y tipo que no es purga; obesidad; trastorno de alimentación compulsiva; trastorno de atracón; y trastorno de alimentación de otra manera no especificado (307.50):

Trastornos de espectro de autismo incluyendo trastorno autístico (299.00), trastorno de Asperger (299.80), trastorno de Rett (299.80), trastorno desintegrador de la niñez (299.10) y trastorno pervasivo de otra manera no especificado (299.80, incluyendo autismo atípico).

Trastorno de déficit de atención/hiperactividad incluyendo los subtipos de tipo combinado de trastorno de déficit de atención/hiperactividad (314.01), tipo predominantemente no atentivo de trastorno de déficit de atención/hiperactividad (314.00), tipo hiperactivo-impulso de trastorno de déficit de atención/hiperactividad (314.01) y trastorno de déficit de atención/hiperactividad de otra manera no especificado (314.9); trastorno hipercinético;trastornos de conducta perturbadora tal como trastorno de conducta incluyendo los subtipos de tipo de inicio en la niñez (321.81), tipo de inicio en la adolescencia (312.82) y tipo de inicio no especificado (312.89), trastorno provocador oposicional (313.81) y trastorno conductual perturbador de otra manera no especificado; y trastornos de tics tales como trastorno de Tourette (307.23):

Trastornos de personalidad incluyendo los subtipos de trastorno de personalidad paranoica (301.0), trastorno de personalidad esquizofrénica

(301.20), trastorno de personalidad esquizotípica (301,22), trastorno de personalidad antisocial (301.7), trastorno de personalidad limítrofe (301,83), trastorno de personalidad histriónica (301.50), trastorno de personalidad narcisista (301,81), trastorno de personalidad de evitación (301.82), trastorno de personalidad dependiente (301.6), trastorno de personalidad obsesivo-compulsiva (301.4) y trastorno de personalidad de otra manera no especificado (301.9):

Aumento de la cognición incluyendo el tratamiento de alteración de la cognición en otras enfermedades tales como esquizofrenia, trastorno bipolar, depresión, otros trastornos psiquiátricos y condiciones psicóticas asociadas con alteración cognitiva, v.gr., enfermedad de Alzheimer; y

Disfunciones sexuales incluyendo trastornos de deseo sexual tales como trastorno de deseo sexual hipoactivo (302.71), y trastorno de aversión sexual (302.79); trastornos de excitación sexual tales como trastorno de excitación sexual femenino (302.72) y trastorno eréctil masculina (302.72); trastornos orgásmicos tales como trastorno orgásmico femenino (302.73), trastorno orgásmico masculino (302.74) y eyaculación prematura (302.75); trastorno de dolor sexual tal como dispareunia (302.76) y vaginismo (306.51); Disfunción sexual de otra manera no especificado (302.70); parafilias tales como exhibicionismo (302.4), fetichismo (302.81), froteurismo (302.89), pedofilia (302.2), masoquismo sexual (302.83), sadismo sexual (302.84), fetichismo transvéstico (302.3), voyeurismo (302.82) y pedofilia de otra manera no especificado (302.9); trastornos de identidad de género tales como

trastornos de identidad de género en niños (302.6) y trastorno de identidad de género en adolescentes o adultos (302.85); y trastorno sexual de otra manera no especificado (302.9).

Todas las diversas formas y subformas de los trastornos aquí mencionados se contemplan como parte de la presente invención.

Por lo tanto, la invención también provee un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo, para usarse como una sustancia terapéutica en el tratamiento o profilaxis de los trastornos psicóticos anteriores, en particular esquizofrenia.

La invención además provee un método de tratamiento de esquizofrenia que comprende administrar a un hospedero que necesita el mismo una cantidad efectiva de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la invención provee el uso de a compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo en la fabricación de un medicamento para usarse en el tratamiento de esquizofrenia.

La invención además provee un método de tratamiento o profilaxis de los trastornos anteriores, en mamíferos incluyendo humanos, que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la invención provee el uso de a compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo en la fabricación

de un medicamento para usarse en el tratamiento de los trastornos anteriores.

Cuando se usan en terapia, los compuestos de la fórmula (I) se formulan generalmente en una composición farmacéutica estándar. Dichas composiciones se pueden preparar usando procedimientos estándares.

Por lo tanto, la presente invención además provee una composición farmacéutica para usarse en el tratamiento de los trastornos anteriores que comprende el compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable.

La presente invención además provee una composición farmacéutica que comprende el compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable.

Los compuestos de la invención se pueden usar en combinación con los siguientes aspectos para tratar o prevenir trastornos psicóticos: i) antipsicóticos; ii) fármacos para efectos colaterales extrapiramidales, por ejemplo anticolinérgicos (tales como benztropina, biperiden, prociclidina y trihexifenidilo), antihistaminas (tales como difenhidramina) y dopaminérgicos (tales como amantadina); iii) antidepresivos; iv) ansiolíticos; y v) incrementadores cognitivos por ejemplo inhibidores de colinesterasa (tales como tacrina, donepezil, rivastigmina y galantamina).

Los compuestos de la invención se pueden usar en combinación con antidepresivos para tratar o prevenir depresión y trastornos del estado de

ánimo.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar o prevenir enfermedad bipolar: i) estabilizadores del estado de ánimo; ii) antipsicóticos; y iii) antidepresivos.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar o prevenir trastornos de ansiedad: i) ansiolíticos; y ii) antidepresivos.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para mejorar abstinencia a la nicotina y y reducir el anhelo a la nicotina: i) terapia de reemplazo de nicotina, por ejemplo, una formulación sublingual de nicotin-beta-ciclodextrina y parches de nicotina; y ii) bupropión.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para mejorar abstinencia al alcohol y reducir el anhelo al alcohol: i) antagonistas de receptor de NMDA por ejemplo acamprosato; ii) agonistas de receptor de GABA, por ejemplo, tetrabamato; y iii) antagonistas de receptor de opioides por ejemplo naltrexona.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para mejorar abstinencia a opiatos y reducir el anhelo a opiatos: i) agonistas de receptor mu de opioides/antagonista de receptor de opioide kappa, por ejemplo, buprenorfina; ii) antagonistas de receptor de opioides, por ejemplo, naltrexona; y iii) antihipertensivos vasodilatadores, por ejemplo, lofexidina.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar o prevenir trastornos del sueño: i) benzodiazepinas, por ejemplo, temazepam, lormetazepam, estazolam y triazolam; ii) hipnóticos que no son benzodiazepina, por ejemplo, Zolpidem, zopiclona, zaleplon e indiplon; iii) barbitúricos, por ejemplo, aprobarbital, butabarbital, pentobarbital, secobarbital y fenobarbital; iv) antidepresivos; v) otros hipnóticos sedantes, por ejemplo, hidrato de cloral y clormetiazol.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar anorexia: i) estimulantes del apetito por ejemplo ciproheptidina; ii) antidepresivos; iii) antipsicóticos; iv) zinc; y v) agentes premenstruales por ejemplo piridoxina y progesteronas.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar o prevenir bulimia: i) antidepresivos; ii) antagonistas de receptor de opioides; iii) antieméticos por ejemplo ondansetrona; iv) antagonistas de receptor de testosterona por ejemplo flutamida; v) estabilizadores del estado de ánimo; vi) zinc; y vii) agentes premenstruales.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar o prevenir autismo: i) antipsicóticos; ii) antidepresivos; iii) ansiolíticos; y iv) estimulantes por ejemplo metilfenidato, formulaciones de anfetamina y pemolina.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar o prevenir ADHD: i) estimulantes por

ejemplo metilfenidato, formulaciones de anfetamina y pemolina; y ii) no estimulantes, por ejemplo, inhibidores de reabsorción de norepinefrina (tales como atomoxetina), agonista de alfa-2 adrenoceptor (tal como clonidina), antidepresivos, modafinil, e inhibidores de colinesterasa (tales como galantamina y donezepil).

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar trastornos de personalidad: i) antipsicóticos; ii) antidepresivos; iii) estabilizadores del estado de ánimo; y iv) ansiolíticos.

Los compuestos de la invención se pueden usar en combinación con los siguientes agentes para tratar o prevenir disfunción sexual masculina: i) inhibidores de fosfodiesterasa V, por ejemplo vardenafil y sildenafil; ii) agonistas de dopamina/inhibidores de transporte de dopamina, por ejemplo, apomorfina y buproprión; iii) antagonistas de alfa adrenoceptor, por ejemplo, fentolamina; iv) agonistas de prostaglandina, por ejemplo, alprostadil; v) agonistas de testosterona tal como testosterona; vi) inhibidores de transporte de serotonina, por ejemplo, inhibidores de reabsorción de serotonina; v) inhibidores de transporte de noradrenalina, por ejemplo, reboxetina y vii) agonistas de 5-HT1A, por ejemplo, flibanserina.

Los compuestos de la invención se pueden usar en combinación con los mismos agentes especificado por disfunción sexual masculina para tratar o prevenir disfunción sexual femenina, y además un agonista de estrógeno tal como estradiol.

Los fármacos antipsicóticos incluyen antipsicóticos típicos (por ejemplo, clorpromazina, tioridazina, mesoridazina, flufenazina, perfenazina, proclorperazina, trifluoperazina, tiotixina, haloperidol, molindona y loxapina); y antipsicóticos atípicos (por ejemplo, clozapina, olanzapina, risperidona, quetiapina, aripirazol, ziprasidona y amisulprido).

Los fármacos antidepresivos incluyen inhibidores de reabsorción de serotonina (tales como citalopram, escitalopram, fluoxetina, paroxetina y sertralina); inhibidores de reabsorción de serotonina/noradrenalina duales (tales como venlafaxina, duloxetina y milnacipran); Los inhibidores de reabsorción de noradrenalina (tales como reboxetina); antidepresivos tricíclicos (tales como amitriptilina, clomipramina, imipramina, maprotilina, nortriptilina y trimipramina); inhibidores de monoamina oxidasa (tales como isocarboxazida, moclobemida, fenelzina y tranilcipromina); y otros (tales como bupropión, mianserina, mirtazapina, nefazodona y trazodona).

Los fármacos de estabilizador del estado de ánimo incluyen valproato de litio, sodio/ácido valproico/divalproex, carbamazepina, lamotrigina, gabapentin, topiramato y tiagabine.

Los ansiolíticos incluyen benzodiazepinas tal como alprazolam y lorazepam.

La invención por lo tanto provee, en un aspecto adicional, una combinación que comprende un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo junto con un agente o agentes terapéuticos adicionales.

Las combinaciones referidas anteriormente se pueden presentar convenientemente para usarse en forma de una formulación farmacéutica y por lo tanto formulaciones farmacéuticas que comprenden una combinación como se definió antes junto con un vehículo farmacéuticamente aceptable o excipiente comprende un aspecto adicional de la invención. Los componentes individuales de dichas combinaciones se pueden administrar ya sea secuencialmente o simultáneamente en formulaciones farmacéuticas separadas o combinadas.

Cuando un compuesto de la fórmula (I) o un derivado farmacéuticamente aceptable del mismo se usa en combinación con un segundo agente terapéutico contra el mismo estado de enfermedad la dosis de cada compuesto puede diferir de aquella cuando el compuesto se usa solo. Las dosis apropiadas serán apreciadas fácilmente por los expertos en la técnica.

Una composición farmacéutica de la invención, que se puede preparar por mezcla, adecuadamente a temperatura ambiente y presión atmosférica, está usualmente adaptada para administración oral, parenteral o rectal y, como tal, puede estar en forma de tabletas, cápsulas, preparaciones líquidas orales, polvos, gránulos, pastillas, polvos reconstituíbles, soluciones o suspensiones para inyección o infusión, o supositorios. Las composición oralmente administrables son generalmente preferidas.

Las tabletas y cápsulas para administración oral pueden estar en forma de dosis unitaria, y pueden contener excipientes convencionales, tales

como agentes aglutinantes, llenadores, lubricantes de tabletas, desintegradores y agentes humectantes aceptables. Las tabletas se pueden revestir de conformidad con métodos bien conocidos en la práctica farmacéutica normal.

Las preparaciones líquidas orales puede estar en forma de, por ejemplo, suspensiones soluciones, emulsiones, jarabes o elíxires acuosos u oleosos, o puede estar en forma de un producto seco para reconstitución con agua u otro vehículo adecuado antes de usarse. Dichas preparaciones líquidas pueden contener aditivos convencionales tales como agentes de suspensión, agentes emulsionantes, vehículos no acuosos (que pueden incluir aceites comestibles), conservadores y, si se desea, saborizantes o colorantes convencionales.

Para administración parenteral, las formas de dosis unitaria se preparan utilizando un compuesto de la invención o sal farmacéuticamente aceptable del mismo y un vehículo estéril. El compuesto, dependiendo del vehículo y la concentración usada, pueden ser ya sea suspendidos o disueltos en el vehículo. Al preparar soluciones, el compuesto se puede disolver para inyección y esterilizar con filtro antes de llenar con el mismo un frasco o ampolleta adecuados y sellar. Ventajosamente, adyuvantes tales como un anestésico local, conservadores y agentes reguladores de pH se disuelven en el vehículo. Para incrementar la estabilidad, la composición se puede congelar después de llenar con la misma el frasco y el agua es removida bajo vacío. Las suspensiones parenterales se preparan sustancialmente de la misma

manera, excepto que el compuesto es suspendido en el vehículo en lugar de ser disuelto, y la esterilización no se puede lograr por filtración.

El compuesto se puede esterilizar por exposición a óxido de etileno antes de la suspensión en un vehículo estéril. Ventajosamente, un agente tensioactivo o agente humectante se incluye en la composición para facilitar la distribución uniforme del compuesto.

Las composiciones adecuadas para administración transdérmica incluyen pomadas, geles y parches.

La composición puede contener de 0.1% a 99% en peso, preferiblemente de 10 a 60% en peso, del material activo, dependiendo del método de administración. La dosis del compuesto usado en el tratamiento de los trastornos antes mencionados variará de la manera usual con la severidad de los trastornos, el peso del paciente, y otros factores similares. Sin embargo, como una guía general, las dosis unitarias adecuadas pueden ser de 0.05 a 1000 mg, muy adecuadamente 1.0 a 200 mg, y dichas dosis unitarias se pueden administrar más de una vez al día, por ejemplo, dos o tres veces al día. Dicha terapia se puede extender un número de semanas o meses.

Sección experimental

Las siguientes descripciones y ejemplos ilustran la preparación de compuestos de la invención.

Los espectros de resonancia magnética de protones (RMN) se

registraron en instrumentos de Varian a 300, 400 ó 500 MHz_1 en el instrumento de Bruker a 300 MHz, los desplazamientos químicos se reportan en ppm (δ) usando la línea de solvente residual como estándar interno. Los patrones de escisión están diseñados como s, singulete; d, doblete; t, triplete; q, cuadriplete; m, multiplete; b, banda ancha. Los espectros de RMN se registraron a temperatura que varió de 25 a 90°C; cuando se detectó más de un conformador los desplazamientos químicos para el más abundante se reporta. Los espectros de masa (EM) se tomaron en un espectrómetro de masa de cudripolo triple 4 II (Micromass UK) o en un espectrómetro de masa Agilent MSD 1100, que operaba en modo de ionización de EA (+) y EA (-) o en un Agilent LC/MSD 1100, que operaba en modo de ionización de EA (+) y EA (-) acoplado con instrumento de CLAR Agilent 1100 Serie [CL/EM - EA (+): análisis realizado en un Supelcosil ABZ + Plus (33x4.6 mm, 3µm) (fase móvil: 100% [agua +0.1 % HCO_2H] durante 1 min, después a partir de 100% [agua +0.1 % HCO_2H] a 5% [agua +0.1 % HCO_2H] y 95% [CH_3CN] en 5 min, finalmente bajo estas condiciones durante 2 min; T=40°C; flujo= 1 ml/min; CL/EMMS - ES (-):análisis realizado en un Supelcosil ABZ ÷Plus (33x4.6 mm, 3 µm) (fase móvil: 100% [agua +0.05% NH_3] durante 1 min, después a partir de 100% [agua +0.05% NH_3 to 5% [agua +0.05% NH_3] y 95% [CH_3CN] en 5 min, finalmente bajo estas condiciones durante 2 min; T=40°C; flujo= 1 ml/min]. En los espectros de masa sólo se reporta un pico en la agrupación de iones moleculares. Las rotaciones ópticas se realizaron a 20°C con un instrumento Jasco DIP360 (1=10 cm, volumen de células = 1 ml, λ = 589 nm)

a menos que se establezca otra cosa. La cromatografía instantánea sobre gel de sílice se llevó a cabo sobre gel de sílice de malla 230-400 suministrado por Merck AG Darmstadt, Alemania o sobre cartuchos pre-empacados Varian Mega Be-Si o sobre cartuchos de sílice Biotage pre-empacados.

CLAR (ascendente) se refiere a análisis de CLAR realizados sobre un Luna C18 (fase móvil: a partir de 100% [agua +0.05%TFA] a 5% [agua +0.05%TFA] y 95% [CH_3CN +TFA 0.05%] en 8 min; T=40°C; flujo= 1 ml/min).

UPLC se refiere a análisis de UPLC realizado en un sistema UPLC Waters Acquity System. UPLC/EM se refiere a análisis de UPLC realizado en un sistema UPLC Waters Acquity System acoplado con un detector de EM Waters ZQ (cuad. individual), intervalo de ms 100-1000. Datos de fase móvil de UPLC:

Gradiente antes del organizador de muestra

A = H_2O + 0.1 % de ácido fórmico

B= MeCN + 0.075% de ácido fórmico

Tiempo (min)	Velocidad de flujo (ml/min)	% de A	% de B	curva
1. Inicial	1.000	97.0	3.0	Inicial
2. 0.10	1.000	94.0	6.0	6
3. 0.60	1.000	30.0	70.0	6
4. 1.10	1.000	1.0	99.0	6
5. 1.45	1.000	97.0	3.0	11

Gradiente después del organizador de muestra (ajustado para dar los mismos tiempos de retención que aquellos logrados antes de la

instalación del organizador de muestra)

Tiempo (min)	Velocidad de flujo (ml/min)	% de A	% de B	curva
1. Inicial	1.000	97.0	3.0	Inicial
2. 0.05	1.000	94.0	6.0	6
3. 0.57	1.000	30.0	70.0	6
4. 1.06	1.000	1.0	99.0	6
5. 1.45	1.000	97.0	3.0	11

curva 6 = gradiente lineal

curve 11 = cambio al final

Waters Acquity 2996 PDA

Longitud de onda de inicio (nm)	210.00
Longitud de onda final (nm)	350.00
Resolución (nm)	2.4
Velocidad de muestreo (espectro/s)	20.000
Respuesta de filtro	0
Tiempo de exposición (ms)	Automático
Interpolate 656	Sí
Tiempo de paro de adqusición (min)	1.50

CCD se refiere a cromatografía de capa delgada sobre placas de gel de sílice de 0.25 mm (60F-254 Merck) y visualizada con luz UV. Para separaciones de fase realizadas usando dispositivos de microfiltración: cartucho de separación de fases con frita de polipropileno de Whatman o Alltech. SCX significa: cartruchos SCX (carga 0.75 mmoles\g) de Varian.

Las soluciones se secaron sobre sulfato de sodio anhidro.

Las siguientes abreviaturas se usan en el texto: AcOEt = acetato de etilo, CH = ciclohexano, DCM = cloruro de metileno, DIPEA = N,N-diisopropiletilamina, DMF = N,N'-dimetilformamida, Et_2O = éter dietílico, EtOH

= etanol, MeOH = metanol, TEA = trietilamina, THF = tetrahidrofurano, TFA = ácido trifluoroacético, CH_3CN= acetonitrilo, std = saturado.

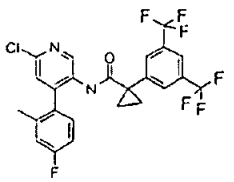
* indica un estereocentro de estereoquímica fija pero desconocida es decir ya sea estereoquímica R o S.

Diastereoisómero 1 o diastereoisómer 2 significa un compuesto de la invención o un intermediario de los mismos como un solo diastereoisómero cuya configuración absoluta en un estereocentro no se determinó.

Enantiómero 1 o enantiómero 2 significa un compuesto de la invención o un intermediario del mismo como un solo enantiómero cuya configuración absoluta no se determinó.

DESCRIPCION 1

1-[3,5-Bis(trifluorometil)fenil]-N-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]ciclopropancarboxamida (D1)



Acido 1-[3,5-Bis(trifluorometil)fenil]ciclopropancarboxílico (400 mg, 1.34 mmoles) se disolvió en diclorometano (6 ml), cloruro de oxalilo (0.24 ml, 2.68 mmoles) se añadió, seguido por dimetilformamida (5 µl, cat.). La solución se agitó durante 3 hr. La solución se concentró bajo vacío. El crudo se disolvió en tolueno, se añadió 6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinamina

(380 mg, 1.61 mmoles), seguido por diisopropiletilamina (0.7 ml, 4 mmoles) y dimetilaminopiridina (164 mg, 1.34 mmoles), y la solución se calentó a 100°C durante la noche. La solución se añadió a acetato de etilo, se lavó con NH_4Cl acuoso saturado y salmuera y se concentró bajo vacío. El producto se aisló por cromatografía (sílice, ciclohexano/EtOAc 90/10 - 80/20) como un sólido blanco: 635 mg, 1.23 mmoles, 92% de rendimiento.

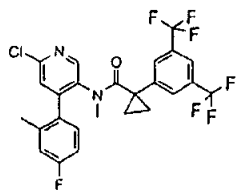
EM (ES/+): m/z = 517 $[M+H]^+$.

RMN ($CDCl_3$): δ (ppm): 9.61 (s, 1 H); 7.79 (s, 1 H); 7.68 (s, 2H); 7.01 (s, 1 H); 6.81-6.68 (m, 3H); 6.43 (s, 1 H); 1.88 (s, 3H); 1.60 (s, 4H)

Rf: 0.35 (ciclohexano/EtOAc 80/20)

DESCRIPCION 2

1-[3,5-Bis(trifluorometil)fenil]-N-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]ciclopropancarboxamida



1-[3,5-Bis(trifluorometil)fenil]-N-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]ciclopropancarboxamida (D1; 310 mg, 0.6 mmoles) se disolvió en dimetilformamida (6 ml). Yoduro de metilo (51.6 µl, 1.2 mmoles) se añadió, seguido por carbonato de cesio (393 mg, 1.2 mmoles), y la suspensión se agitó durante la noche). La suspensión se dividió entre acetato de etilo y

NH_4Cl acuoso saturado, y la fase orgánica se lavó con salmuera y se concentró bajo vacío. El producto se aisló por cromatografía (sílice, ciclohexano/EtOAc 90/10 - 80/20) como un sólido blanco: 300 mg, 0.56 mmoles, 93% de rendimiento.

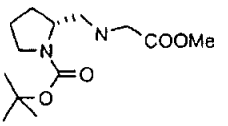
EM (ES/+): m/z = 531 $[M+H]^+$.

RMN (DMSO-d_6): δ (ppm) 8.34 (s, 1 H); 7.88 (s, 1 H); 7.70 (s, 2H); 7.40 (s, 1 H); 7.06 (dd, 1H), 6.90 (m, 2H); 2.97 (s, 3H), 2.11 (s, 3H), 1.21-1.37 (m, 4H)

Rf: 0.3 (ciclohexano/EtOAc 80/20)

DESCRIPCION 3

(2*R*)-2-({[2-(metiloxi)-2-oxoetil]amino}metil)-1-pirrolidincarboxilato de 1,1-dimetiletilo (D3)



(2*R*)-2-formil-1-pirrolidincarboxilato de 1,1-dimetiletilo (1 g, 5.02 mmoles) se disolvió en 20 ml de dicloroetano anhidro. Clorhidrato de glicinato de metilo (0.95 g, 7.57 mmoles) se añadió, seguido después de 30 min por triacetoxiborhidruro de sodio (2.2 g, 10.38 mmoles). La reacción se agitó durante 8 hr a temperatura ambiente. La mezcla de reacción se diluyó con metanol para obtener una solución clara, que se hizo pasar a través de un cartucho de SCX. El producto se eluyó con amoniaco metanólico 1 M. El

producto se aisló por cromatografía (sílice, diclorometano/metanol 95/5) como aceite incoloro: 800 mg, 2.94 mmoles.

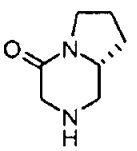
EM (ES/+): m/z = 273 $[M+H]^+$.

RMN ($CDCl_3$): δ (ppm): 4.01 (bs, 1 H); 3.75 (s, 3H); 3.53-3.30 (m, 4H); 2.94-2.53 (m, 3H); 1.92-1.76 (m, 3H); 1.48 (s, 9H).

Rf: 0.40 (ciclohexano/EtOAc 1/1)

DESCRIPCION 4

(8a*R*)-Hexahidropirrolo[1,2-a]pirazin-4(1H)-ona (D4)



(2*R*)-2-({[2-(metiloxi)-2-oxoetil]amino}metil)-1-pirrolidincarboxilato de 1,1-dimetiletilo (D3; 800 mg, 2.94 mmoles) se disolvió en cloruro de metileno (10 ml) y se trató con ácido trifluoroacético (2.5 ml) durante 2 hr. La mezcla de reacción se cargó como tal en una columna SCX y los compuestos no básicos se lavaron con metanol. Las fracciones de ninhidrina-positivas eluídas con amoniaco metanólico 1 M se concentraron bajo vacío a 40°C durante 30 min, aislando el compuesto del título como un aceite amarillo pálido: 410 mg, 2.92 mmoles, 99% de rendimiento.

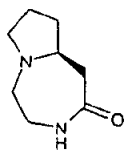
EM (ES/+): m/z = 141 $[M+H]^+$.

RMN (DMSO-d_6): δ (ppm) 3.69 (q, 1H), 3.62-3.45 (m, 3H), 3.45-3.35 (m, 2H), 2.52 (t, 1H), 2.13-1.96 (m, 2H), 1.85-1.72 (m, 1H), 1.50-1.37 (m,

1 H).

DESCRIPCION 5

(9a*S*)-Hexahidro-1*H*-pirrolo[1,2-*d*][1,4]diazepin-2(3*H*)-ona (D5)



Clorhidrato de (2*S*)-2-pirrolidinilacetato de metilo (1.08 g, 6.04 mmoles) se disolvió en 20 ml de dicloroetano anhidro. Se añadió (2-oxoetil)carbamato de 1,1-dimetiletilo (1.2 g, 7.25 mmoles), seguido después de 30 min por triacetoxiborhidruro de sodio (2.68 g, 12.08 mmoles). La reacción se agitó durante 3 hr a temperatura ambiente. La mezcla de reacción se diluyó con metanol para obtener una solución clara, que se hizo pasar a través de un cartucho de SCX. El producto se eluyó con amoniaco metanólico 1 M. El solvente se removió bajo presión reducida dejando el producto como un aceite amarillo pálido. El crudo se disolvió en cloruro de metileno (20 ml) y se trató con ácido trifluoroacético (5 ml) durante 1 hr. La mezcla de reacción se cargó como tal en una columna SCX y los compuestos no básicos se lavaron con metanol. Las fracciones de ninhidrina-positivas eludías con amoniaco metanólico 1 M se concentraron. El residuo se volvió a disolver en acetonitrilo (20 ml) y se agitó a 60°C durante 2 hr. El solvente se removió bajo presión reducida y el producto se purificó por cromatografía (sílice, CH_2Cl_2/MeOH 95/5, Rf= 0.4) y se aisló como un sólido blanco: 315 mg, 2.04

mmoles, 34% de rendimiento.

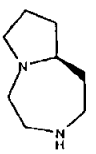
EM (ES/+): 155 $[M+H]^+$.

RMN (DMSO-d_6): δ (ppm) 7.50 (bs, 1H), 3.35-3.21 (m, 1H), 3.05-2.95 (m, 2H), 2.56-2.43 (m, 2H), 2.26-2.11 (m, 2H), 2.08-1.96 (m, 2H), 1.94-1.83 (m, 1H), 1.72-1.52 (m, 2H), 1.41-1.29 (m, 1H).

Rf: 0.2 (diclorometano/metanol 95/5)

DESCRIPCION 6

(9a*S*)-Octahidro-1*H*-pirrolo[1,2-*d*][1,4]diazepina (D6)



Solución de complejo de borano-tetrahidrofurano (1 M, 17.8 ml) se añadió a una solución de (9a*S*)-hexahidro-1*H*-pirrolo[1,2-*d*][1,4]diazepin-2(3*H*)-ona (D5; 160 mg, 1.04 mmoles) en tetrahidrofurano (5 ml) a 0°C y la mezcla se agita a temperatura ambiente durante 30 min. Se añadió lentamente solución de HCl-agua (6N, 20 ml) a 0°C y la solución se calentó a 60°C durante 4 hr. El solvente se removió bajo presión reducida y el producto se aisló por elución con amoniaco metanólico 1 M a partir de un cartucho de SCX (aceite pardusco, 120 mg, 83% de rendimiento).

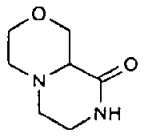
EM (ES/+): m/z = 141 $[M+H]^+$.

RMN (DMSO-d_6): δ (ppm): 7.55 (bs, 1H), 3.65-3.09 (m, 3H), 3.08-2.82 (m, 2H), 2.55-2.39 (m, 2H), 2.38-2.27 (m, 1H), 2.27-2.09 (m, 1H), 2.08-

1.79 (m, 2H), 1.78-1.48 (m, 2H), 1.47-1.27 (m, 2H).

DESCRIPCION 7

Hexahidropirazino[2,1-*c*][1,4]oxazin-9(6*H*)-ona (D7)



A una suspensión agitada de ácido morfolin-2-carboxílico de N-Boc (991 mg, 4.29 mmoles) en 10 ml de éter dietílico se añadió una solución de trimetilsilildiazometano (4 ml, 2M en hexanos, 8 mmoles). Después de la adición de metanol, el material de partida se puso en solución y se observó la evolución vigorosa de nitrógeno gaseoso. Después de 1 hr 30 min, un análisis de CCD mostró desaparición completa del material de partida. El solvente se removió bajo presión reducida, dejando el producto crudo como un aceite (1.3 g), que contenía tanto el éster metílico como el éster trimetilsililmetílico esperados (EM (ES/+): m/z=268 $[M+Na]^+$, 146 $[M-BoC]^+$, 340 $[M+TMS+Na]^+$, 218 $[M+TMS-Boc]^+$. El crudo se disolvió en cloruro de metileno (10 ml) y se trató con ácido trifluoroacético (2.5 ml) durante 1 hr 30 min. Los compuestos de amina libre se obtuvieron recogiendo las fracciones de ninhidrina-positivas eluidas con amoniaco metanólico 1 M a partir de una columna SCX. Después de la remoción del solvente, el crudo (aceite amarillo pálido, 670 mg, EM (ES/+): m/z=146 $[M+H]^+$, 218 $[M+TMS+H]^+$) se hizo reaccionar con N-boc-2-aminoacetaldehído (756 mg, 4.75 mmoles) en 1,2-dicloroetano anhidro (13 ml)

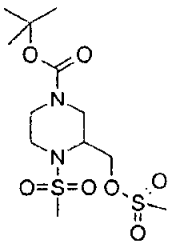
en presencia de triacetoxiborhidruro de sodio (1.8 g, 8.44 mmoles) durante 16 hr bajo atmósfera de nitrógeno. La reacción se diluyó con metanol y se cargó en una columna SCX. Las fracciones eluidas con amoniaco metanólico 1 M se concentraron. El aceite crudo residual (880 mg, EM (ES/+): m/z=289 $[M+H]^+$, 361 $[M+TMS+H]^+$) se disolvió en cloruro de metileno anhidro (12 ml) y se trató con 4 ml de TFA durante 30 min a 0°C y a temperatura ambiente durante 3 hr. La mezcla de reacción se cargó como tal en una columna SCX y los compuestos no básicos se lavaron con metanol. Las fracciones de ninhidrina-positivas eluidas con amoniaco metanólico 1 M se concentraron. El residuo se volvió a disolver en metanol (20 ml) y se agitó a 40°C durante 30 min. El solvente se removió bajo presión reducida y el producto se purificó por cromatografía (sílice, CH_2Cl_2/MeOH 95/5, Rf= 0.25) y se aisló como un sólido blanco: 395 mg obtenidos (2.53 mmoles).

EM (ES/+): 157 $[M+H]^+$, 179 $[M+Na]^+$.

RMN ($CDCl_3$): δ (ppm) 5.77 (br.s, 1 H); 4.32 (dd, 1 H); 3.87 (br.d, 1H); 3.70 (t, 1H); 3.63 (td, 1H); 3.53 (t, 1H); 3.30-3.22 (m, 2H); 2.98-2.86 (m, 1H); 2.80 (d, 1H); 2.63 (td, 1H); 2.49 (td, 1H).

DESCRIPCION 8

4-(Metilsulfonil)-3-{[(metilsulfonil) oxi]metil}-1-piperazincarboxilato de 1,1-dimetiletilo (D8)



A una solución de 4.65 g de 3-(hidroximetil)-1-piperazinacarboxilato de 1,1-dimetiletilo en 30 ml de diclorometano seco, bajo N_2 a 0°C, se añadieron 4.75 ml de TEA, seguido por la adición lenta de 3.7 ml de cloruro de metansulfonilo. Después de 12 hr de agitación vigorosa a temperatura ambiente, la mezcla de reacción se recogió con diclorometano/H_2O, las fases se separaron y la fase acuosa se extrajo nuevamente con diclorometano. Los compuestos orgánicos recogidos se secaron sobre Na_2SO_4 y se concentraron bajo vacío para dar material crudo que se purificó por cromatografía sobre sílice eluyendo con diclorometano/MeOH a partir de 100/0 a 90/10 para dar 4 g del material del título puro como espuma incolora.

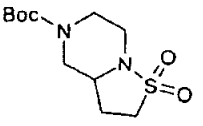
Rf (DCM/MeOH 9/1) = 0.8

^{1}H RMN ($CDCl_3$) δ: 1.48 (s, 9H), 2.96 (bs, 1H), 2.98 (s, 3H), 3.08 (s, 3H), 3.11 (bs, 1H), 3.2 (td, 1H), 3.71 (d, 1H), 4.02 (bs, 1H), 4.12 (bd, 1H), 4.23 (bm, 1H), 4.3 (bm, 1H), 4.4 (bm, 1H).

240

DESCRIPCION 9

1,1-Dióxido de hexahidro-5*H*-isotiazol[2,3-a]pirazin-5-carboxilato de 1,1-dimetiletilo



A una solución de 4 g de 4-(metilsulfonil)-3-{[(metilsulfonil) oxi]metil}-1-piperazincarboxilato de 1,1-dimetiletilo (D8) en 50 ml de THF seco, bajo N_2 a -78°C, se añadieron gota a gota 11.8 ml de secBu-Li 1 M en THF. Después de 30 min, la mezcla se dejó alcanzar lentamente la temperatura ambiente. Después de 2.5 hr, la reacción se extinguió con 20 ml de agua, se recogió con 100 ml de acetato de etilo y las fases se separaron. La fase acuosa se extrajo nuevamente con acetato de etilo (2 x 50 ml). Los compuestos orgánicos recogidos se secaron sobre Na_2SO_4 y se concentraron bajo vacío para dar material crudo que se purificó por cromatografía sobre sílice eluyendo con ciclohexanoy/EtOAc a partir de 7/3 a 6/4 para obtener, después de la evaporación del solvente, 2.438 g de del material del título puro como un sólido blanco.

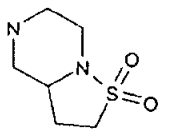
Rf (Cy/EA 1/1) = 0.45

EM (ES/+): 177 (M-Boc), 221 (M-iBu), 299 ($M+Na^+$).

^{1}H RMN ($CDCl_3$) δ: 1.49 (s, 9H), 2.02 (m, 1H), 2.42 (m, 1H), 2.67 (bs, 1H), 2.81 (td, 1H), 2.95 (bs, 1H), 3.15 (m, 1H), 3.18 (m, 1H), 3.27 (td, 1H), 3.41 (d, 1H), 4.17 (b, 1H), 4.32 (b, 1H).

DESCRIPCION 10

1,1-Dióxido de hexahidro-2*H*-isotiazol[2,3-*a*] pirazina (D10)



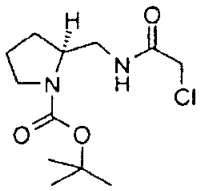
A una solución de 1.5 g de 1,1-dióxido de hexahidro-5*H*-isotiazol[2,3-*a*]pirazin-5-carboxilato de 1,1-dimetiletilo (D9) en 20 ml de diclorometano seco, bajo N_2 a 0°C, se añadieron gota a gota 5 ml de TFA y se dejó que reaccionara a 0°C durante 1 hr. Después, la mezcla de reacción se evaporó bajo vacío y el material sólido crudo se purificó por cartucho SCX 50 g, cargando con DCM/MeOH, lavando con DCM/MeOH, después sólo con MeOH; el producto se recuperó eluyendo con NH_3 1 M en MeOH. La evaporación del solvente dio 0.95 g de compuesto del título puro como sólido blanco.

EM (ES/+): 177 $[M+H]^+$

^1H RMN ($CDCl_3$) δ: 1.97 (m, 1H), 2.36 (m, 1H), 2.59 (dd, 1H), 2.80 (dd, 2H), 3.1 (m. 3H), 3.19 (m, 2H), 3.41 (m, 1H).

DESCRIPCION 11

(2*S*)-2-{[(cloroacetil)amino]metil}-1-pirrolidincarboxilato de 1,1-dimetiletilo (D11)



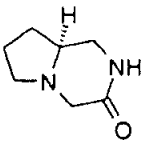
DIPEA (1.34 ml, 7.5 mmoles) se añadió a una solución de (2*S*)-2-(aminometil)-1-pirrolidincarboxilato de 1,1-dimetiletilo (1 g, 5 mmoles) en 50 ml de DCM; después, cloruro de cloroacetilo (0.418 ml, 5.25 mmoles) se añadió lentamente y la mezcla de reacción se agitó durante 1 hr antes de ser tratada. Se añadió DCM y la fase orgánica se lavó con una solución saturada de cloruro de amonio. El crudo se purificó por cromatografía instantánea eluyendo con ciclohexano/acetato de etilo 8/2 dando 1.24 g del material objetivo.

EM (ES/+): 299-301 $[M + Na]^+$

RMN ($CDCl_3$): δ (ppm) 8.43-8.28 (br.s., 1H), 4.03 (s, 2H), 3.76-3.65 (m, 1H), 3.31-3.14 (m, 3H), 3.15-3.04 (m, 1H), 1.89-1.60 (m, 4H), 1.40 (s, (H).

DESCRIPCION 12

(8a*S*)-Hexahidropirrol[1,2-*a*]pirazin-3(4*H*)-ona (D12)



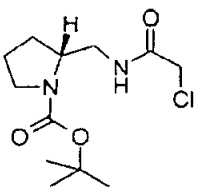
(2*S*)-2-{[(cloroacetil)amino]metil}-1-pirrolidincarboxilato de 1,1-dimetiletilo (D11; 1.24, 4.5 mmoles), se disolvió en 20 ml de DCM y se trató con TFA (5 ml) a temperatura ambiente. Después de 1 hr, se observó la conversión completa en el material deseado y la mezcla de reacción se cargó en un cartucho de SCX. El producto obtenido después de la elución con NH_3 2M en MeOH, se disolvió después en acetonitrilo (30 ml) y se trató con carbonato de sodio (1.43 g, 10.34 mmoles). La mezcla de reacción se calentó a 60°C durante 6 horas; el crudo obtenido después de la remoción se purifica por cromatografía instantánea eluyendo con diclorometano/MeOH 95/5 dando 310 mg.

EM (ES/+): 141 $[M+H]^+$

RMN ($CDCl_3$): δ (ppm) 7.80-7.59 (br. s, 1H), 3.38 (d, 1H), 3.28-3.17 (m,1H), 2.99 (dt, 1H), 2.89 (t, 1H), 2.69 (d, 1H), 2.30-2.17 (m, 1H), 2.06-1.96 (m, 1H), 1.92-1.80 (m, 1H), 1.81- 1.71 (m, 2H), 1.41-1.29 (m, 1H).

DESCRIPCION 13

(2*R*)-2-{[(cloroacetil)amino]metil}-1-pirrolidincarboxilato de 1,1-dimetiletilo



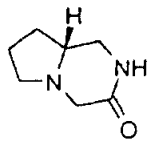
DIPEA (1.34 ml, 7.5 mmoles) se añadió a una solución de (2*R*)-2-(aminometil)-1-pirrolidincarboxilato de 1,1-dimetiletilo (1 g, 5 mmoles) en 50 ml de DCM; después cloruro de cloroacetilo (0.418 ml, 5.25 mmoles) se añadió lentamente y la mezcla de reacción se agitó durante 1 hr antes de ser tratada. Se añadió DCM y la fase orgánica se lavó con una solución saturada de cloruro de amonio. El crudo se purificó por cromatografía instantánea eluyendo con ciclohexano/acetato de etilo 8/2 dando 1.28 g del material objetivo.

EM (ES/+): 299-301 $[M + Na]^+$

RMN ($CDCl_3$): δ (ppm) 8.43-8.28 (br.s., 1H), 4.03 (s, 2H), 3.76-3.65 (m, 1H), 3.31-3.14 (m, 3H), 3.15-3.04 (m, 1H), 1.89-1.60 (m, 4H), 1.40 (s, (H).

DESCRIPCION 14

(8a*R*)-Hexahidropirrolo[1,2-a]pirazin-3(4*H*)-ona (D14)



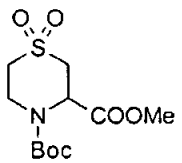
(2*R*)-2-{[(cloroacetil)amino]metil}-1-pirrolidincarboxilato de 1,1-dimetiletilo (D13; 1.24 g, 4.5 mmoles), se disolvió en 20 ml de DCM y se trató con TFA (5 ml) a temperatura ambiente. Después de 1 hr, se observó la conversión completa en el material deseado y la mezcla de reacción se cargó en un cartucho de SCX. El producto obtenido después de la elución con NH_3 2M en MeOH se disolvió después en acetonitrilo (30 ml) y se trató con carbonato de sodio (1.43 g, 10.34 mmoles). La mezcla de reacción se calentó a 60°C durante 6 horas; el crudo obtenido después de la remoción se purifica por cromatografía instantánea eluyendo con diclorometano/MeOH 95/5 dando 250 mg del compuesto deseado.

EM (ES/+): 141 $[M+H]^+$

RMN ($CDCl_3$): δ (ppm) 7.80-7.59 (br. s, 1H), 3.38 (d, 1H), 3.28-3.17 (m,1H), 2.99 (dt, 1H), 2.89 (t, 1H), 2.69 (d, 1H), 2.30-2.17 (m, 1H), 2.06-1.96 (m, 1H), 1.92-1.80 (m, 1H), 1.81- 1.71 (m, 2H), 1.41-1.29 (m, 1H).

DESCRIPCION 15

1,1-Dióxido de 3,4-tiomorfolindicarboxilato de 4-(1,1-dimetiletil) 3-metilo (D15)



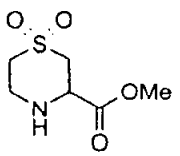
La preparación se hizo en dos lotes. En el primero, a una solución agitada de 3,4-tiomorfolindicarboxilato de 4-(1,1-dimetiletil) 3-metilo (WO 2001/040185) (936 mg, 3.59 mmoles) en 3 ml de diclorometano se añadió ácido 3-cloroperbenzoico al 55% (2.353 g, 7.50 mmoles) a 0°C mientras se agitaba bajo atmósfera de nitrógeno. Se dejó que la reacción alcanzara temperatura ambiente en 1 hr. Se añadió una alícuota adicional de ácido 3-cloroperbenzoico al 55% (500 mg, 1.59 mmoles) y la reacción se agitó durante 15 min. La solución de reacción se lavó con bicarbonato de sodio acuoso saturado y tiosulfato de sodio. La fase orgánica se secó sobre Na_2SO_4 y el solvente se removió dejando el producto crudo, 1.01 g. En el segundo lote, se aplicó el mismo procedimiento para convertir 714 mg (3.59 mmoles) de 3,4-tiomorfolindicarboxilato de 4-(1,1-dimetiletil) 3-metilo usando 2.134 g de ácido 3-cloroperbenzoico al 55% (6.80 mmoles) en 5 ml de diclorometano, obteniendo 1.23 g de producto crudo. Las reacciones crudas combinadas se purificaron por cromatografía (sílice, ciclohexano/acetato de etilo 70/30) para dar 1.73 g del compuesto objetivo.

EM (ES/+): 316 $[M+Na]^+$, 194 $[M-Boc+1]^+$.

RMN (DMSO-d_6): δ (ppm) 5.55-5.17 (ms, 1H); 4.41-4.21(dt, 1H); 3.73-3.63 (m, 3H); 3.62- 3.35 (m, 3H); 3.28-3.10 (td, 1H); 3.10-2.96 (dd, 1H); 1.56-1.24 (m, 9H).

DESCRIPCION 16

1,1-Dióxido de 3-tiomorfolincarboxilato de metilo (D16)



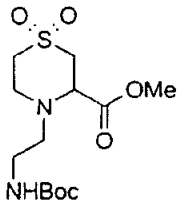
A una solución de 1,1-dióxido de 3,4-tiomorfolindicarboxilato de 4-(1,1-dimetiletil) 3-metilo (D15; 1.73 g, 5.9 mmoles) en 17 ml de cloruro de metileno anhidro, se añadió gota a gota ácido trifluoroacético (4.2 ml) mientras se agitaba a 0°C bajo atmósfera de nitrógeno. La solución se agitó durante 3 hr, mientras se dejó que alcanzara temperatura ambiente. El solvente se removió bajo presión reducida y el residuo se cargó sobre un cartucho de SCX, se lavó con metanol y se eluyó con amoniaco metanólico 0.5M. Las fracciones básicas se recogieron y el solvente se removió dejando 1.08 g del producto objetivo.

EM (ES/+): 194 $[M+Na]^+$

RMN (DMSO-d_6): δ (ppm) 4.14-3.92 (br s, 1H); 3.84-3.70 (dd, 1H); 3.65-3.59 (s, 3H); 3.34-3.15 (m, 2H); 3.11-2.99 (m, 1H); 3.11-2.78 (m, 2H); 3.05-2.80 (m, 1H).

DESCRIPCION 17

1,1-Dióxido de 4-[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]-3-tiomorfolincarboxilato de metilo (D17)



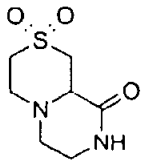
A una solución agitada de 1,1-dióxido de 3-tiomorfolincarboxilato de metilo (D16; 1.08 g, 5.6 mmoles) en 14 ml de 1,2-dicloroetano anhidro se añadió N-boc-2-aminoacetaldehído (1.1 g, 6.7 mmoles) y ácido acético (0.316 ml, 5.6 mmoles). Despues de 30 min, se añadió triacetoxiborhidruro de sodio (1.78 g, 8.4 mmoles) y la solución se agitó a temperatura ambiente. Alícuotas adicionales de N-boc-2-aminoacetaldehído y triacetoxiborhidruro de sodio (1.0 g, 4.7 mmoles) se añadieron y la reacción se continuó durante la noche. El solvente se removió bajo presión reducida y el residuo se purificó por columna de SCX, seguido por cromatografía (sílice, ciclohexano:acetato de etilo 70:30 a 1:1) y nievamente SCX, para dar 295 mg del compuesto objetivo.

EM (ES/+): 337 $[M+1]^+$.

RMN (DMSO-d_6): δ (ppm) 6.77-6.55 (m, 1H), 4.17-4.08 (m, 1H), 3.69-3.57 (s, 3H), 3.48-3.31 (m, 3H); 3.17-2.89 (m, 5H); 2.80-2.71 (m, 1H); 2.70-2.61 (m, 1H); 1.44-1.29 (s, 9H).

DESCRIPCION 18

2,2-Dióxido de hexahidropirazino[2,1-*c*][1,4]tiazin-9(6*H*)-ona (D18)



A una solución de 1,1-dióxido de 4-[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]-3-tiomorfolincarboxilato de metilo (D17; 295 mg, 0.88 mmoles) en 3 ml de diclorometano anhidro se añadió 1 ml de ácido trifluoroacético y la solución resultante se agitó a temperatura ambiente bajo nitrógeno durante 1 hr 30 min. El solvente se removió bajo presión reducida y el residuo se cargó en una columna SCX, se lavó con metanol y se eluyó con amoniaco metanólico. El producto se purificó adicionalmente por cromatografía (cartucho de sílice, ciclohexano a acetato de etilo, después diclorometano a diclorometano:metanol 70:30) para dar 165 mg del compuesto objetivo.

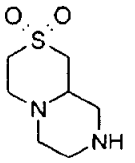
EM (ES/+): 205 $[M+1]^+$

RMN (DMSO-d_6): δ (ppm) 8.14-8.08 (br.s, 1H), 3.36-3.27 (m, 2H), 3.26-3.19 (m, 2H), 3.19- 3.15 (m, 1H); 3.13-3.04 (m, 3H); 2.99-2.92 (dd, 1H); 2.68-2.61 (m, 1H); 2.59-2.52 (dt, 1H).

DESCRIPCION 19

300

2,2-Dióxido de octahidropirazino[2,1-c][1,4]tiazina (D19)



A una suspensión de 2,2-dióxido de hexahidropirazin[2,1-*c*][1,4]tiazin-9(6H)-ona (D18; 165 mg, 0.81 mmoles) en 1 ml de THF anhidro se añadieron sucesivamente alícuotas de una solución 1 M de complejo de borano-THF en THF (total 20.4 ml, 20.4 mmoles) y la reacción se agitó a temperatura ambiente y 50°C, hasta la desaparición del material de partida. Acido clorhídrico (5M, 2 ml) se añadió a la solución y la agitación se continuó a 50°C durante 12 hr. El solvente se removió bajo presión reducida y el residuo se cargó sobre un cartucho de SCX, se lavó con metanol y se eluyó con amoniaco metanólico 0.5M. Las fracciones básicas se recogieron y el solvente se removió dejando 172 mg del producto objetivo, parcialmente contaminado por el material de partida.

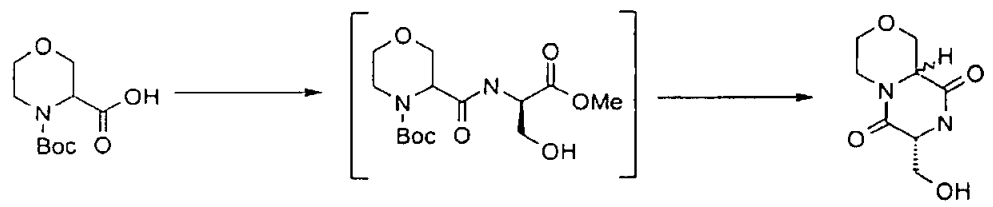
EM (ES/+): 191 $[M+1]^+$.

RMN (CD_3OD): δ (ppm) 3.50-2.70 (m, 13H); 2.42-2.33 (dt, 1H).

DESCRIPCION 20

(7*R*, 9a*R*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]oxazin-6,9-diona y (7*R*,9a*S*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]oxazin-6,9-diona

(D20)



Acido morfolin-2-carboxílico de N-Boc (Astatech, 1.34 g, 5.80 mmoles) se suspendió en 15 ml de diclorometano anhidro, y se trató con tetrafluoroborato de *O*-benzotriazol-1-il-*N,N,N'N'*-tetrametiluronio (TBTU) (2.4 g, 7.47 mmoles) y diisopropiletilamina (2 ml, 11.47 mmoles). La reacción se agitó durante 40 min. Una solución de clorhidrato de éster D-serinmetílico (1.8 g, 11.57 mmoles) y diisopropiletilamina (2 ml, 11.47 mmoles) en diclorometano (15 ml) se preparó y se añadió a la mezcla de reacción. La reacción se dejó agitar a temperatura ambiente durante la noche. Análisis de UPLC-EM mostró conversión al producto. La reacción se diluyó con diclorometano (40 ml) y se extrajo con $NaHCO_3$ saturado (2 x 40 ml), se secó (Na_2SO_4), y el solvente se removió. El crudo se recogió para el siguiente paso sin purificación adicional.

Este se disolvió en 20 ml de diclorometano y se trató con 10 ml de TFA. La reacción se agitó a temperatura ambiente y se verificó por UPLC-EM después de 4 hr, lo cual mostró la desaparición del pico para el material de partida, reemplazado por uno nuevo para las especies desprotegidas (m/z=

233, M+1). La mezcla de reacción se cargó como tal sobre un cartucho de SCX, se lavó con MeOH (4 volúmenes de columna) y se eluyó con amoniaco metanólico 0.5 M. Las fracciones básicas, ninhidrina-positivas se recogieron y el solvente se removió. El residuo se disolvió en 10 ml de MeOH y se agitó a 50°C bajo N_2 durante la noche (16 hr). La reacción se enfrió y se formó un precipitado, que se recogió por filtración para dar 370 mg del compuesto del título.

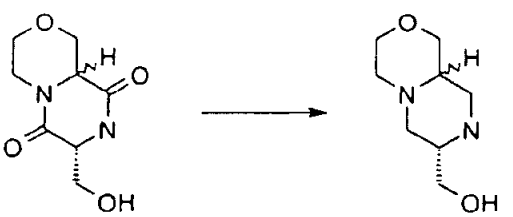
EM directa: m/z= 223 (M+Na).

^{1}H-RMN: consistente con la estructura. Relación de aprox. 60:40 de diaestereoisómeros:

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.17-8.26 (s, 0.4 H) 8.09-8.17 (s, 0.6 H) 5.17-5.25 (m, 0.4 H) 5.09-5.17 (m, 0.6 H) 3.95-4.29 (m, 3 H) 3.60-3.91 (m, 3 H) 3.33-3.55 (m, 2H) 2.61-2.90 (m, 0.6 H) 1.03-1.15 (t, 0.4 H).

DESCRIPCION 21

(7*S*, 9a*R*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol y (7*S*, 9a*S*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol (D21)



(7*R*, 9a*R*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-6,9-diona y (7*R*, 9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-6,9-diona

(D20) (365 mg, 1.82 mmoles) se trataron con 20 ml de solución de BH_3-THF 1M a temperatura ambiente. La suspensión se puso a reflujo durante 17 hr y se verificó por EM directa, mostrando la conversión completa al producto. Esta se enfrió a 0°C, y 2 ml de MeOH se añadieron lentamente, seguido por 1 ml de HCl concentrado (a pH <1). La solución se calentó a 70°C, se agitó durante 2 hr y se verificó por EM directa. La solución se llevó a temperatura ambiente, el solvente se removió y el residuo se recogió en MeOH (se añadieron unas pocas gotas de agua), se cargó sobre un cartucho de SCX, se lavó con MeOH (5 volúmenes de columna) y se eluyó con amoniaco metanólico 2M. Las fracciones de ninhidrina-positivas se recogieron y el solvente se removió, dejando el producto del título como un aceite claro. 320 mg. EM directa: m/z= 173 (M+1).

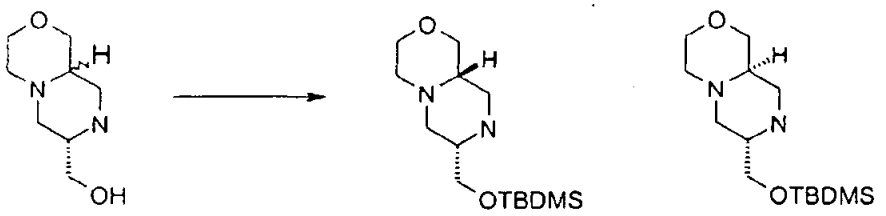
^{1}H-RMN consistente con la estructura, parece ser una mezcla de diaestereómeros en una relación de aprox. 60:40:

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 4.50-4.59 (m, 0.4 H) 4.38-4.48 (m, 0.6 H) 2.96-3.74 (m, 6 H) 2.57-2.78 (m, 2H) 2.34-2.41 (m, 2H) 1.86-2.28 (m, 4 H) 1.69 (t, 1H)

DESCRIPCION 22 y DESCRIPCION 23

(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D22) y

(7*S*,9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D23)



D22 D23

(7*S*, 9a*R*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol y (7*S*, 9a*S*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol (D21) (315 mg, 1.83 mmoles) se disolvieron en 10 ml de diclorometano anhidro y se trataron con Et_3N (600 µl, 4.30 mmoles) y TDBMSCl (590 mg, 3.91 mmoles). La reacción se agitó durante la noche a temperatura ambiente (17 hr). Esta se diluyó con diclorometano (30 ml) y se extrajo con $NaHCO_3$ saturado (2 x 20 ml). Análisis de CCD (EtOAc:MeOH 95:5) mostró 2 productos principales. Los compuestos orgánicos se secaron y el solvente se removió dejando un aceite, que se purificó por cromatografía instantánea (sílice, EtOAc→EtOAc:MeOH 90:10). Se aislaron dos productos: (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil] oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D22), 253 mg. EM directa: m/z= 287 (M+1).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 3.72-3.79 (m, 1H) 3.62-3.71

(m, 2H) 3.37-3.56 (m, 2H) 2.99 (t, 1H) 2.65-2.78 (m, 1H) 2.55-2.64 (m, 1H) 2.25-2.44 (m, 3 H) 2.02-2.16 (m, 2H) 1.90-2.02 (m, 1H) 0.75-0.90 (s, 9 H) -0.05-0.05 (s, 6 H).

Identificado como el isómero *cis* con base en los picos cruzados de ROESY.

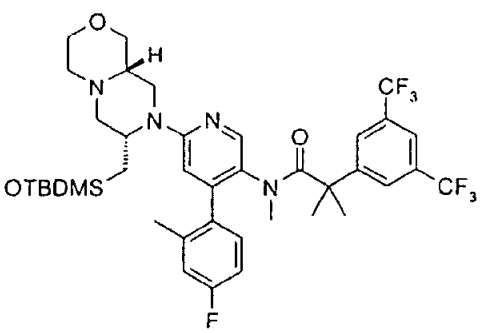
(7*S*,9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-pirazino[2,1-*c*][1,4]oxazina (D23), 202 mg. EM directa: m/z= 287 (M+1).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 3.68 (d, 1H) 3.56 (d, 1H) 3.47 (t, 1H) 3.36-3.43 (m, 2H) 3.02 (t, 1H) 2.68-2.76 (m, 1H) 2.62-2.68 (m, 2H) 2.50-2.56 (m, 1H) 2.22 (t, 1H) 2.11-2.18 (m, 1H) 1.90-1.97 (m, 1H) 1.70 (t, 1H) 0.84 (s, 9 H) 0.02 (s, 6 H)

Identificado como el isómero *trans* con base en los picos cruzados de ROESY.

DESCRIPCION 24

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1H)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D24)



Método a):

(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-pirazino[2,1-*c*][1,4]oxazina (D22) (250 mg, 0.872 mmoles) se disolvió en 3.8 ml de tolueno. A esta solución se añadió 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (460 mg, 0.863 mmoles), seguido por bis-tri-ter-butilfosfinopaladio (110 mg, 0.215 mmoles), cloruro de hexadeciltrimetilamonio (45 µl de una solución acuosa al 25%) y solución de hidróxido de sodio (85 µl de una solución acuosa al 50%, 0.85 mmoles). La solución se desgasificó mediante 3 ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C. Después de 4 hr, análisis de UPLC/EM indicó la conversión del compuesto objetivo y sin rastros de cloropiridina de partida. La reacción se llevó a temperatura ambiente, se diluyó con EtOAc (20 ml) y se lavó con $NaHCO_3$ saturado (10 ml). Los compuestos orgánicos se secaron y el solvente se evaporó. El producto se aisló por cromatografía instantánea (ciclohexano -> ciclohexano:EtOAc 85:15) como un sólido blanco: 390 mg (0.498 mmoles, 57%) se tomaron para el siguiente paso sin caracterización adicional.

Método b):

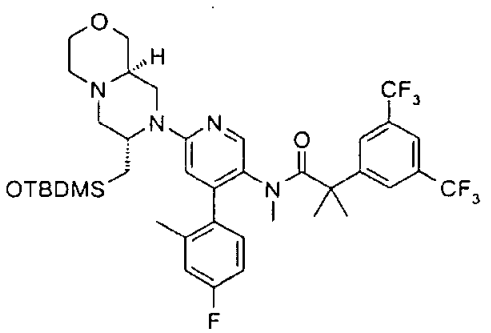
A una solución agitada de (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil) silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D107, 5 g, 17.45 mmoles) en 150 ml de tolueno seco a temperatura ambiente bajo nitrógeno, se añadió una solución de 2-[3,5-bis(trifluorometil)fenil]-N-[6-cloro-4-(4-fluoro-2-

metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (7.75 g, 14.54 mmoles) en 50 ml de tolueno seco, seguido por ter-butóxido de sodio (2.1 g, 21.81 mmoles) y bis(tri-ter-butilfosfin)paladio (1.49 g, 2.908 mmoles). La mezcla resultante se calentó a temperatura de reflujo durante 4 horas. La mezcla se dejó enfriar a temperatura ambiente y se filtró sobre Sterimat. El filtrado después se diluyó con acetato de etilo (200 ml) y con bicarbonatos de sodio (solución sat., 200 ml). Las fases se separaron y la capa acuosa se extrajo con acetato de etilo (2 x 150 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo vacío a un residuo, se purificaron por cromatografía de gel de sílice eluyendo con 10 a 20% de EtOAc/Ciclohexano para dar el compuesto del título como espuma amarillo pálido (10.1 g). UPLC/EM: pico a Rt = 1.26 min con m/z = 783.35 $[M+H]^+$

CLAR (ascendente): Rt = 6.98 min (% de área = 98.22)

DESCRIPCION 25

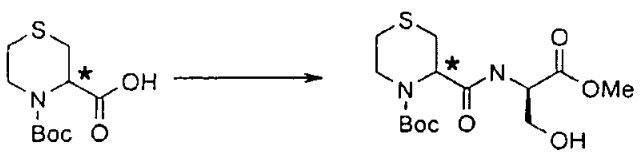
2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D25)



(7*S*,9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-pirazin[2,1-*c*][1,4]oxazina (D23) (140 mg, 0.489 mmoles) se disolvió en 2 ml de tolueno. A esta solución se añadió 2-cloropiridina (236 mg, 0.444 mmoles), seguido por bis-tri-ter-butilfosfinopaladio (60 mg, 0.117 mmoles), cloruro de hexadeciltrimetilamonio (25 µl de una solución acuosa al 25%) y solución de hidróxido de sodio (45 µl de una solución acuosa al 50%). La solución se desgasificó mediante 3 ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C. El análisis de UPLC/EM después de 4 hr, indicó sólo conversión parcial al compuesto objetivo. Se añadió más catalizador (20 mg, 0.039 mmoles) y la reacción se dejó a la misma temperatura durante 2 hr adicionales, pero no se observó cambio en la conversión al producto. La solución se diluyó con EtOAc (20 ml) y se lavó con $NaHCO_3$ saturado (10 ml). El producto se aisló por cromatografía instantánea (ciclohexano:EtOAc 94:6 → 50:50) como un aceite amarillo pálido: 87 mg (0.111 mmoles, 23%) se tomaron para el siguiente paso sin caracterización adicional.

DESCRIPCION 26

(3*R* o *S*)-({[(1*R*)-1-(hidroximetil)-2-(metiloxi)-2-oxoetil]amino}carbonil)-4-tiomorfolincarboxilato de 1,1-dimetiletilo (nombre no preferido) (D26)-diaestereoisómero 1



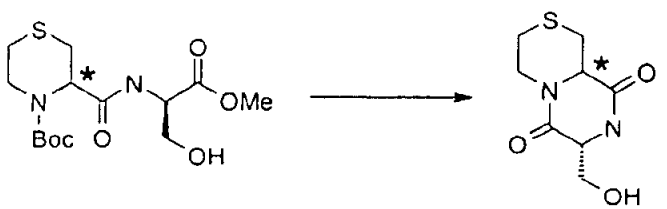
A una solución de ácido tiomorfolincarboxílico de N-Boc (0.488 g, 1.97 mmoles) y tetrafluoroborato de *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (TBTU) (0.697 g, 2.17 mmoles) en 5 ml de diclorometano anhidro se añadió DIPEA (0.7 ml, 3.95 mmoles) y la solución se agitó durante 30 min. A una suspensión de clorhidrato de éster D-serinmetílico (0.47 g, 3.95 mmoles) en 5 ml de diclorometano anhidro se añadió DIPEA (0.7 ml, 3.95 mmoles) y la solución resultante se agitó durante 30 min. Después la solución que contenía la base libre de serina se añadió a la mezcla de reacción y ésta se dejó agitar a temperatura ambiente durante la noche.

Se añadió agua a la mezcla de reacción y las dos fases se separaron. La capa acuosa se extrajo con diclorometano (3X) y las fases orgánicas combinadas se secaron (Na_2SO_4) y se evaporaron a sequedad. Este material crudo (1.66 g) se usó en el siguiente paso sin purificación adicional.

UPLC-EM: m/z= 349 (M+1) a t=0.59 min

DESCRIPCION 27

(7*R*, 9a*R* o 9a*S*)-7-(hidroximetil)hexahidropirazin[2,1-c][1,4]tiazin-6,9-diona (D27)-Diaestereoisómero 1 de (D32)



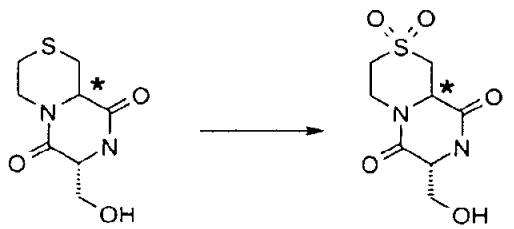
A una solución de (3*R* o *S*)-({[(1*R*)-1-(hidroximetil)-2-(metiloxi)-2-oxoetil]amino}carbonil)-4-tiomorfolincarboxilato de 1,1-dimetiletilo crudo (D26) en 20 ml de diclorometano se añadieron 10 ml de TFA. La mezcla de reacción se agitó a temperatura ambiente durante 4 hr. El solvente se removió bajo presión reducida y el residuo se recogió en MeOH y se cargó sobre un cartucho de SCX. Las fracciones eluidas con amoniaco metanólico se recogieron, el volumen se redujo y la solución se agitó a 50°C durante 45 min. Después, se irradió tres veces por microondas [parámetros establecidos: T=80°C, t=10 min (1X); T=120°C, t=5 min (2X)]. El solvente se removió y después de 2 días, el crudo reveló la formación de un sólido blanco. Por lo que se precipitó con DME y se recogió por filtración, lavando con Et_2O, para dar el 1er. lote del compuesto del título (120 mg, rendimiento = 28% en 2 pasos). La solución filtrada se evaporó a sequedad y el crudo resultante, disuelto en DME, se irradió dos veces por microondas (parámetros establecidos: T=130°C, t=30 min). Después de filtración, el 2do. lote del compuesto del título se aisló como un sólido pardusco (94 mg, rendimiento =22% en 2 pasos). La solución filtrada se trató de la misma manera que antes y después de cuatro irradiaciones por microondas [parámetros establecidos: T=130°C, t=30 min (3X) y t=90 min (1X)] el 3er. lote del compuesto del título se aisló como un sólido pardusco (50 mg, rendimiento =12% en 2 pasos). Puesto que la pureza de estos tres lotes fue muy similar por análisis de RMN, todos se usaron en el siguiente paso.

UPLC/EM: m/z= 217 (M+1) a t=0.36 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.03-8.27 (m, 1H) 5.04 (t, 1H) 4.73 (td, 1H) 3.98 (dd, 1H) 3.86-3.90 (m, 1H) 3.72-3.79 (m, 1H) 3.47-3.57 (m, 1H) 2.90 (d, 1H) 2.80 (d, 1H) 2.73-2.81 (m, 1H) 2.45-2.64 (m, 2H).

DESCRIPCION 28

2,2-Dióxido de (7*R*, 9a*R* o 9a*S*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]tiazin-6,9-diona (D28)-Diaestereoisómero 1 de (D33)



A una suspensión de la (7*R*, 9a*R* o 9a*S*)-7-(hidroximetil)-hexahidropirazino[2,1-*c*][1,4]tiazin-6,9-diona de partida (D27) (264 mg, 1.22 mmoles) en diclorometano (5 ml) se añadió m-CPBA al 77% (684 mg, 3.05 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 3 hr. El solvente se removió y el crudo se purificó por cromatografía (sílice, CH_2Cl_2:NH_3 2M en MeOH 95:5 a 8:2) para dar el compuesto del título como un sólido blanco (200 mg, rendimiento =66%).

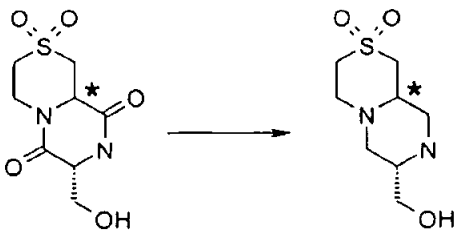
CLAR/EM: m/z= 249 (M+1) a t=0.21 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.34-8.47 (m, 1H) 5.11 (t, 1H) 4.80 (dt, 1H) 4.25 (dd, 1H) 3.89-3.99 (m, 1H) 3.72-3.84 (m, 1H) 3.62 (t, 1H) 3.49-3.59 (m, 1H) 3.23-3.37 (m, 2H) 3.13 (t, 1H) 3.01 (t, 1H)

DESCRIPCION 29

[(7*S*, 9a*R* o 9a*S*)-2,2-dioxidooctahidropirazino[2,1-*c*][1,4]tiazin-7-il]metanol

(D29)-Diaestereoisómero 1 de (D34)



A una solución del 2,2-dióxido (7*R*, 9a*R* o 9a*S*)-7-(hidroximetil)-hexahidropirazino[2,1-*c*][1,4]tiazin-6,9-diona de partida (D28) (200 mg, 0.806 mmoles) se añadió 8.06 ml de solución de BH_3-THF 1M a temperatura ambiente. La suspensión se puso a reflujo durante la noche y se verificó por UPLC/EM.

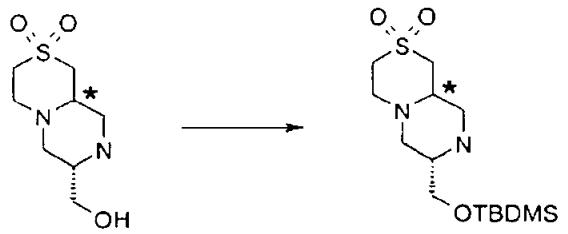
HCl 6 N (aprox. 8 ml) se añadió a la mezcla de reacción, se enfrió a 0°C, y la solución resultante se puso a reflujo durante 1 hr. El crudo se purificó por cartucho de SCX para dar el compuesto del título como un sólido blanco (182 mg, rendimiento cuantitativo)

CLAR/EM: m/z= 221 (M+1) a t=0.17 min

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 4.56 (t, 1H) 3.18-3.26 (m, 2H) 2.94-3.15 (m, 4 H) 2.72-2.80 (m, 3 H) 2.56-2.64 (m, 1H) 2.44-2.53 (m, 1H) 2.22-2.36 (m, 2H) 1.74 (t, 1H).

DESCRIPCION 30

2,2-Dióxido de (7*S*, 9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi} metil)octahidropirazino[2,1-*c*][1,4]tiazina (D30)-Diaestereoisómero 1



A una suspensión de [(7*S*, 9a*R* o 9a*S*)-2,2-dioxidooctahidropirazin[2,1-*c*][1,4]tiazin-7-il]metanol (D29) (182 mg, 0.818 mmoles) en 8 ml de diclorometano anhidro se añadió Et_3N (340 µl, 2.45 mmoles) y TDBMSCl (246 mg, 1.64 mmoles). La mezcla de reacción se agitó durante 15 hr a temperatura ambiente y después la solución homogénea se dejó sin agitar durante 2 días.

Se añadió $NaHCO_3$ saturado y las dos fases se separaron. La capa acuosa se extrajo con diclorometano (3X) y las fases orgánicas combinadas se secaron con Na_2SO_4 y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice, CH_2Cl_2:MeOH 1:0 a 99:1) para dar el compuesto del título como un sólido blanco (150 mg, rendimiento = 55%).

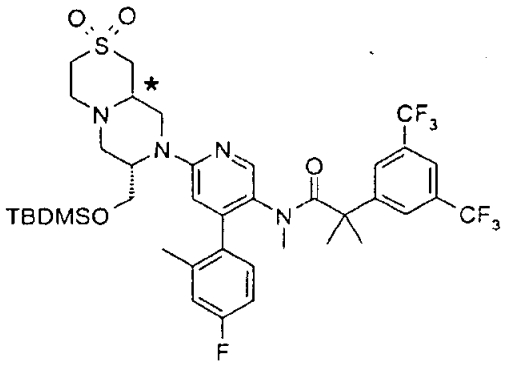
UPLC/EM: m/z= 335 (M+1) a t=0.54 min

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.39-3.48 (m, 1H) 3.31-3.40 (m, 1H) 3.13 (t, 1H) 2.91- 3.09 (m, 3 H) 2.70-2.85 (m, 3 H) 2.56-2.65 (m, 1H) 2.42-2.51 (m, 1H) 2.27-2.36 (m, 1H) 2.19-2.30 (m, 1H) 1.91-2.06 (m, 1H) 1.74 (t, 1H) 0.80 (s, 9 H) -0.02 (s, 6H)

DESCRIPCION 31

2-[3,5-bis(trifluorometil)fenil]-N-[6-[(7*S*, 9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2,2-dioxidohexahidropirazin[2,1-*c*][1,4]tiazin-8(1H)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida

(D31)-Diaestereoisómero 1



A una solución de 2,2-dióxido de (7*S*, 9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)dimetil)silil]oxi}metil)ooctahidropirazino[2,1-*c*][1,4]tiazina (D30) (147 mg, 0.44 mmoles) y 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (180 mg, 0.338 mmoles) en 3 ml de tolueno anhidro se añadieron bis-tri-ter-butilfosfinopaladio (34.5 mg, 0.068 mmoles), cloruro de hexadeciltrimetilamonio (21.6 µl, de una solución acuosa al 25%) y solución de hidróxido de sodio (40 µl, de una solución acuosa al 50%). La mezcla de reacción se desgasificó por ciclos de congelamiento-bombeo-descongelamiento y solvente se agitó a 90°C durante 12 hr. Durante este tiempo de reacción, se añadieron cantidades adicionales del catalizador de paladio (17+17 mg). EtOAc y $NaHCO_3$ se añadieron a la mezcla de reacción y

las dos fases se separaron. La fase acuosa se extrajo con EtOAc (3X) y las fases orgánicas combinadas se secaron (Na_2SO_4) y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice, ciclohexano: EtOAc 9:1 a 75:25) para dar el compuesto del título como un sólido blanco (172 mg, rendimiento = 47%).

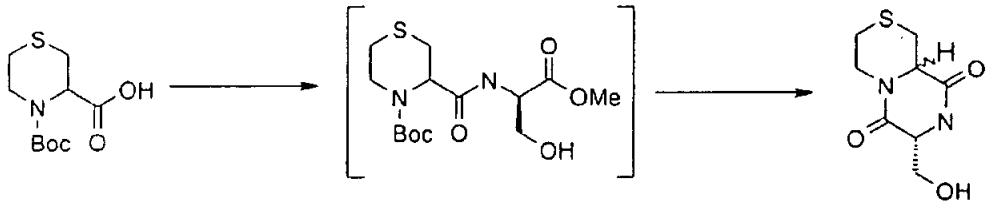
EM: m/z= 831 (M+1) y 416 ($^{M}/_{2}$ +1)

CLAR/EM: m/z= 831 (M+1) y 416 ($^{M}/_{2}$ +1) a t=1.22 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.86 (s, 1H) 7.60-7.82 (m, 2H) 7.16 (d, 1H) 6.98-7.14 (m, 2H) 6.67 (s, 1H) 4.36-4.54 (m, 1H) 3.91-4.12 (m, 1H) 3.80-3.94 (m, 1H) 3.58-3.73 (m, 1H) 3.08-3.47 (m, 5 H) 2.87-3.00 (m, 1H) 2.72-2.82 (m, 1H) 2.51 (s, 3 H) 2.42-2.67 (m, 3 H) 2.19 (s, 3 H) 1.49 (s, 3 H) 1.34 (s, 3 H) 0.78 (s, 9 H) 0.00 (s, 6 H).

DESCRIPCION 32

(7*R*, 9a*R*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]tiazin-6,9-diona y (7*R*, 9a*S*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]tiazin-6,9-diona (D32)



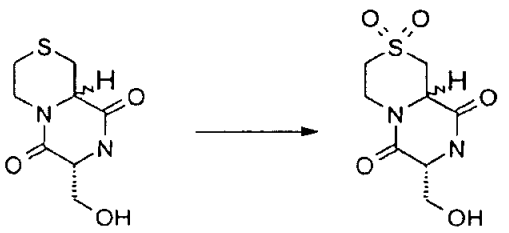
A una solución de ácido tiomorfolincarboxílico de N-Boc (0.803 g, 2.96 mmoles) en 16 ml de diclorometano anhidro se añadió tetrafluoroborato de *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (TBTU) (1.03 g, 3.22 mmoles)

y la solución se agitó durante 45 min. Se preparó una solución de clorhidrato de éster D-serinmetílico (0.911 g, 5.85 mmoles) y base de Huenig (1.02 ml, 5.85 mmoles) en diclorometano y se añadió a la mezcla de reacción. La reacción se dejó agitar a temperatura ambiente durante la noche. El análisis de UPLC-EM mostró conversión al producto. La reacción se diluyó con diclorometano y se extrajo con agua, se secó (Na_2SO_4), y el solvente se removió. El crudo (1.73 g) se recogió para el siguiente paso sin purificación adicional.

Este se disolvió en 60 ml de diclorometano y se añadieron 15 ml de TFA a 0°C. La reacción se agitó a temperatura ambiente durante 2 hr. El solvente se removió bajo presión reducida y el residuo se recogió en MeOH y se cargó sobre un cartucho de SCX. Las fracciones que provienen de SCX se recogieron, el solvente se removió y el residuo se disolvió en metanol y se agitó a 50°C durante la noche, después a 90°C durante 21 hr. La reacción se enfrió mantenida en un congelador. El precipitado que se formó se recogió por filtración y la solución madre se concentró removiendo el solvente. Las dos fracciones se analizaron por ^{1}H-RMN, que fue consistente con el producto, como una mezcla de diaestereoisómeros. Se combinaron y se usaron en el siguiente paso sin purificación adicional.

DESCRIPCION D33

2,2-Dióxido de (7*R*, 9a*R*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]tiazin-6,9-diona y 2,2-dióxido de {7*R*, 9a*S*)-7-(hidroximetil)hexahidropirazin [2,1-*c*][1,4]tiazin-6,9-diona (D33)

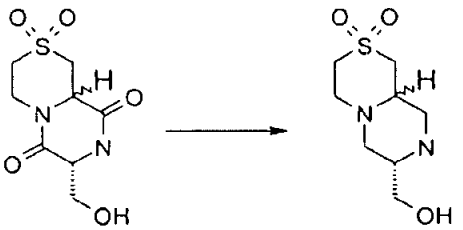


A una suspensión de (7*R*, 9a*R*)-7-(hidroximetil)hexahidropirazin [2,1-*c*][1,4]tiazin-6,9-diona y (7*R*, 9a*S*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]tiazin-6,9-diona (D32) (851 mg, 3.94 mmoles) en diclorometano (17 ml), se añadió m-CPBA al 77% (2.21 g, 9.84 mmoles) y la reacción se dejó a temperatura ambiente durante 2 hr. Se formó un precipitado y se separó y se lavó con MeOH. La fase líquida se concentró. El producto se aisló por cromatografía instantánea (CH_2Cl_2 → CH_2Cl_2: NH_3 0.5M en MeOH 85:15), obteniendo 594 mg, 2.39 mmoles.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.44 (s, 1H) 8.41 (s, 1H) 5.48 (t, 1H) 5.12 (t, 1H) 4.80 (dt, 1H) 4.70-4.76 (m, 2H) 4.37 (dd, 1H) 4.25 (dd, 1H) 4.07-4.12 (m, 1H) 3.89-3.99 (m, 1H) 3.72-3.85 (m, 2H) 3.62 (t, 1H) 3.52-3.57 (m, 1H) 3.23-3.47 (m, 4 H) 2.95-3.18 (m, 6 H). Mezcla de diaestereoisómeros (relación de aproximadamente 55/45).

DESCRIPCION 34

[(7*S*, 9a*R*)-2,2-dioxidooctahidropirazino[2,1-*c*][1,4]tiazin-7-il]metanol y [(7*S*, 9a*S*)-2,2-dioxidooctahidropirazino[2,1-*c*][1,4]tiazin-7-il]metanol (D34)



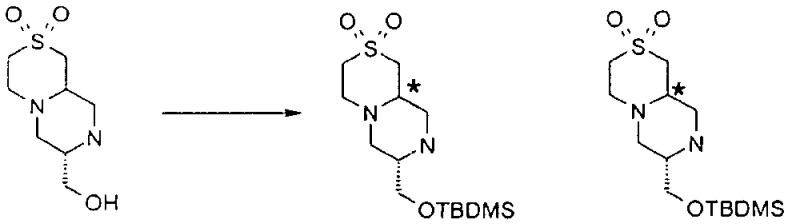
A 2,2-dióxido de (7*R*, 9a*R*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]tiazin-6,9-diona y 2,2-dióxido de (7*R*, 9a*S*)-7-(hidroximetil)hexahidropirazin[2,1-*c*][1,4]tiazin-6,9-diona (D33) (592 mg, 2.39 mmoles) se añadieron 24 ml de solución de BH_3-THF 1M a temperatura ambiente. La suspensión se puso a reflujo durante la noche, y se verificó por UPLC/EM: los picos de producto vistos a 0.17 y 0.37 min, ambos con m/z= 221 (M+1).El exceso de BH_3 se extinguió mediante la adición de MeOH (10 ml) a 0°C, seguido por HCl concentrado (2 ml) y la solución se calentó a 80°C y se agitó durante 4 hr. El crudo se purificó por cartucho de SCX, dejando el producto esperado: 398 mg, 1.81 mmoles.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 4.50 (t, 1H) 4.60 (t, 1H) 3.33-3.43 (m, 2H) 2.99-3.29 (m, 12H) 2.75-2.93 (m, 2H) 2.56-2.72 (m, 2H) 2.25-2.38 (m, 3 H) 1.76 (t, 1H).

La muestra consiste de una mezcla de diaestereoisómeros (relación de aproximadamente 60/40).

DESCRIPCION 35 y DESCRIPCION 30

2,2-Dióxido de (7*S*, 9a*S* o *R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil) octahidropirazino[2,1-*c*][1,4]tiazina (D35)- diaestereoisómero 2 y 2,2-dióxido de (7*S*, 9a*R* o *S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil) octahidropirazino[2,1-*c*][1,4]tiazina (D30)-diaestereoisómero 1



A una solución del aminoalcohol de partida (397 mg, 1.80 mmoles) en 9 ml de diclorometano anhidro se añadió Et_3N (880 µl, 6.31 mmoles) y TDBMSCl (815 mg, 5.41 mmoles). La reacción se agitó durante la noche a temperatura ambiente. Esta se verificó por UPLC/EM: pico para los productos a 0.56 min, m/z = 335 (M+1). Se diluyó con diclorometano y se extrajo con $NaHCO_3$ saturado. Los compuestos orgánicos se secaron (Na_2SO_4) y el solvente se removió. El crudo se purificó por cromatografía instantánea (sílice, CH_2Cl_2 → CH_2Cl_2: MeOH 90:10). Se aislaron dos productos:

2,2-Dióxido de (7*S*, 9a*S* o *R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi} metil)octahidropirazino[2,1-*c*][1,4]tiazina (D35)- diaestereoisómero 2

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 3.49-3.59 (m, 2H) 2.99-3.20 (m, 3 H) 2.79-2.92 (m, 3 H) 2.63-2.77 (m, 3 H) 2.54-2.63 (m, 2H) 2.20-2.28 (m, 1H) 0.78-0.87 (m, 9 H) -0.05-0.04 (m, 6 H)

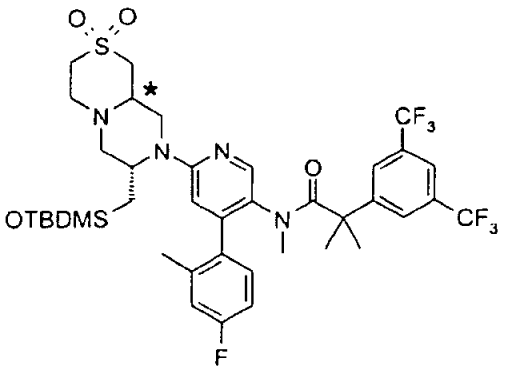
320

2,2-Dióxido de (7*S*, 9a*R* o *S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi} metil)octahidropirazino[2,1-*c*][1,4]tiazina (D30)-diaestereoisómero 1

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 3.43-3.50 (m, 1H) 3.36-3.43 (m, 1H) 3.11-3.23 (m, 1H) 2.96-3.11 (m, 3 H) 2.74-2.86 (m, 3 H) 2.59-2.69 (m, 1H) 2.23-2.39 (m, 2H) 1.95-2.10 (m, 1H) 1.77 (t, 1H) 0.80-0.89 (m, 9 H) -0.03-0.06 (m, 6 H) consistente con el diaestereómero obtenido previamente (D30)

DESCRIPCION 36

2-[3,5-Bis(trifluorometil)fenil]-N-[6-[(7*S*, 9a*S* o *R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2,2-dioxidohexahidropirazin[2,1-*c*][1,4]tiazin-8(1H)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D36)-Diaestereómero 2

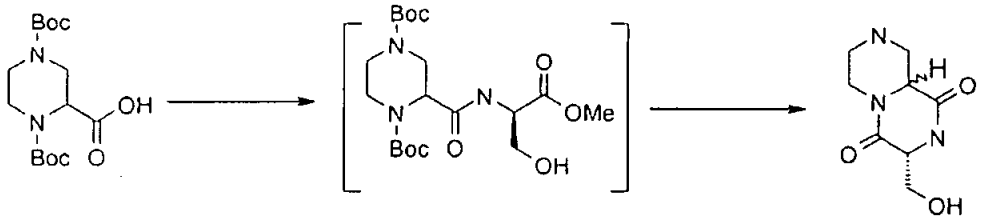


A una solución de 2,2-dióxido de (7*S*, 9a*S* o *R*)-7-({[(1,1-dirnetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]tiazina (D35) (111 mg, 0.331 mmoles) en 2.2 ml de tolueno se añadieron 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetil-propanamida [WO 2005/002577] (136 mg, 0.254 mmoles), bis-tri-ter-

butilfosfinpaladio (26 mg, 0.051 mmoles), cloruro de hexadeciltrimetilamonio (16 µl de una solución acuosa al 25%) y, por último, solución de hidróxido de sodio (31 µl de una solución acuosa al 50%). La solución se desgasificó por ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C durante 3.5 he. Una verificación por UPLC/EM mostró el pico del producto a 1.22 min., m/z = 831 (M+1), 416 (M/2 +1). La solución se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado, y los compuestos orgánicos se secaron (Na_2SO_4). El producto se aisló por cromatografía instantánea (ciclohexano:EtOAc 100:0 → 40:60): 160 mg (0.192 mmoles) se tomaron para el siguiente paso sin caracterización adicional.

DESCRIPCION 37

(3*R*, 9a*R*)-3-(hidroximetil)tetrahidro-2*H*-pirazino[1,2-a]pirazin-1,4(3*H*,6*H*)-diona y (3*R*, 9a*S*)-3-(hidroximetil)tetrahidro-2H-pirazino[1,2-a]pirazin-1,4(3*H*,6*H*)-diona (D37)



A una solución de ácido 1,4-bis{[(1,1-dimetiletil)oxi]carbonil}-piperazincarboxílico (10.88 g, 32.93 mmoles) en 100 ml de diclorometano se añadió tetrafluoroborato de *O*-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio (TBTU) (11.62 g, 36.19 mmoles) y diisopropiletilamina (8.6 ml, 54.28 mmoles).

La reacción se agitó durante 1 hr. Mientras tanto, se preparó una solución de clorhidrato de éster D-serinmetílico (10.24 g, 65.81 mmoles) y diisopropiletilamina (11.50 ml, 65.9 mmoles) en diclorometano y finalmente se añadió a la mezcla de reacción. La reacción se dejó agitar a temperatura ambiente durante 2.5 hr. El análisis de UPLC-EM no mostró más material de partida y conversión al producto (pico a 0.67 min, m/z = 432, M+1). La reacción se diluyó con diclorometano y se extrajo con $NaHCO_3$ saturado, se secó (Na_2SO_4), y el solvente se removió. El crudo (23.5 g) se recogió para el siguiente paso sin purificación adicional.

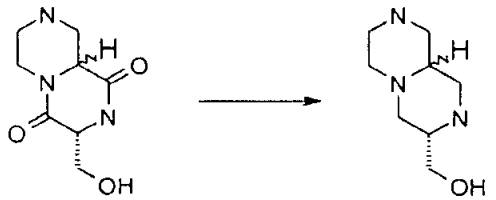
Este se disolvió en 80 ml de diclorometano y se trató con 20 ml de TFA, añadidos a 0°C. La reacción se agitó a temperatura ambiente durante 2 hr, se almacenó en un congelador durante la noche, y después se añadió nuevamente con 10 ml de TFA y se agitó a temperatura ambiente durante 8 hr. Se almacenó nuevamente en el congelador, después se añadió más TFA (20 ml) y se agitó a temperatura ambiente durante 5 hr. Después de la adición a 0°C de 30 ml de TFA y calentamiento a 30°C durante 3 hr, la reacción pareció, por UPLC/EM, no contener ya material de partida. El producto visto a 0.20 min, m/z = 232 (M+1). El volumen de la reacción se redujo por evaporación y el crudo se purificó por SCX. Las fracciones básicas se agitaron a 50°C durante la noche. La solución se concentró y el residuo sólido se trituró con MeOH (5 ml) y éter dietílico, dejando 4.44 g de producto. Mezcla (2:1) de dos diaestereómeros.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.02-8.07 (s, 0.66 H) 7.98-

8.02 (s, 0.33 H) 5.00-5.21 (m, 1H) 4.14-4.33 (m, 1H) 3.67-3.89 (m, 3 H) 3.41-3.55 (m, 1H) 3.10-3.29 (m, 2H) 2.76-2.94 (m, 1H) 2.26-2.68 (m, 3 H).

DESCRIPCION 38

(3*S*, 9a*R*)-octahidro-2*H*-pirazino[1,2-a]pirazin-3-ilmetanol y (3*S*, 9a*S*)-octahidro-2*H*-pirazino[1,2-a]pirazin-3-ilmetanol (D38)

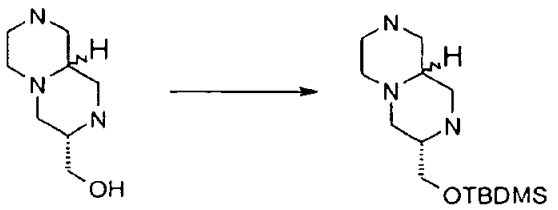


(3*R*, 9a*R*)-3-(hidroximetil)tetrahidro-2H-pirazino[1,2-a]pirazin-1,4(3*H*,6*H*)-diona y (3*R*, 9a*S*)-3-(hidroximetil)tetrahidro-2*H*-pirazin[1,2-*a*] pirazin-1,4(3*H*,6*H*)-diona (D37) (4.44 g, 22.28 mmoles) se dividió en dos porciones iguales. Cada porción se trató a 0°C con 110 ml de solución de BH_3-THF 1M y llevando a reflujo (80°C) durante 24 hr. La reacción se verificó por UPLC/EM directo y no se completó. Una alícuota adicional de 50 ml de solución de BH_3-THF 1M se añadió a cada reacción, y se mantuvieron a 80°C durante 16 hr adicionales. Se verificaron nuevamente por EM y se encontró que que estaban completas (para ambas m/z= 172, M+1). Los matraces de reacción se enfriaron a –10°C y se trataron con 30 ml de HCl 6M. Las soluciones resultantes se calentaron a 80°C y se agitaron durante 3.5 hr. Amabas reacciones se verificaron por EM directa (m/z= 172, M+1 para ambas muestras). La mezcla de reacción se purificó por SCX, obteniendo 4.07 g de

producto. 1H RMN fue consistente con la estructura, mezcla de diaestereoisómeros.

DESCRIPCION 39

(3*S*, 9a*R*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-2*H*-pirazino[1,2-a]pirazina y (3*S*, 9a*S*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-2H-pirazino[1,2-a]pirazina (D39)



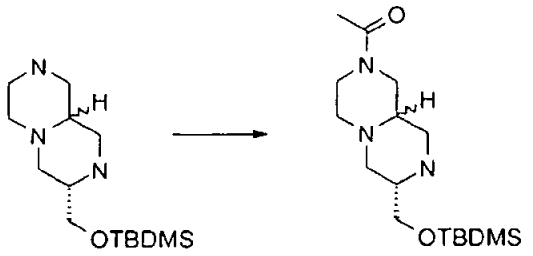
(3*S*, 9a*R*)-octahidro-2*H*-pirazino[1,2-a]pirazin-3-ilmetanol y (3*S*, 9a*S*)-octahidro-2*H*-pirazino[1,2-a]pirazin-3-ilmetanol (D38) (4.065 g, 23.75 mmoles) se disolvió en 100 ml de diclorometano y se trató con Et_3N (9.32 ml, 71.25 mmoles) y TDBMSCl (8.4 g, 59.38 mmoles). La reacción se agitó a temperatura ambiente durante 70 hr. Se verificó por UPLC/EM, que mostró conversión a producto: picos a 0.45 y 0.46 min, m/z = 286 (M+1). Se diluyó con diclorometano, se extrajo con $NaHCO_3$ saturado y salmuera, y se secó sobre Na_2SO_4. El crudo se purificó por cromatografía instantánea (sílice, $CH_2Cl_2 \rightarrow CH_2Cl_2$: MeOH 80:20), para dar 4.410 g de el producto esperado. El espectro fue consistente con el producto. Mezcla de diaestereómeros, relación aproximada de 2:1.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.67-3.81 (m, 1H) 3.35-3.48

(m, 1H) 2.58-2.84 (m, 5 H) 2.18-2.58 (m, 3 H) 1.93-2.17 (m, 2H) 1.74-1.93 (m, 1H) 1.63-1.74 (m, 1H) 0.87 (s, 3 H) 0.86 (s, 6 H) 0.04 (2, 2H) 0.02 (s, 4 H).

DESCRIPCION 40

(7*S*, 9a*R*)-2-acetil-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-2*H*-pirazino[1,2-a]pirazina y (7*S*, 9a*S*)-2-acetil-7-({[(1,1-dimetiletil)(dimetil) silil]oxi}metil)octahidro-2*H*-pirazino[1,2-a]pirazina (D40)



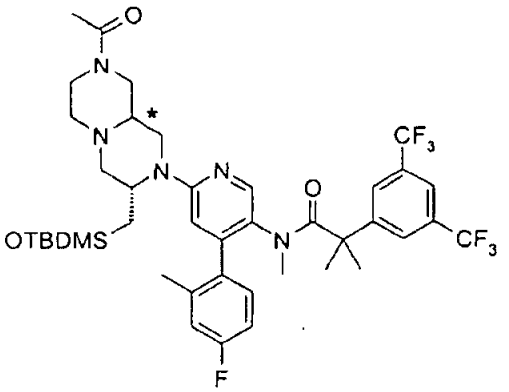
A una solución de (3*S*, 9a*R*)-3-({[(1,1-dimetiletil)(dimetil) silil]oxi}metil)octahidro-2*H*-pirazino[1,2-a]pirazina y (3*S*, 9a*S*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-2*H*-pirazino[1,2-a]pirazina (D39) (4.407 g, 15.44 mmoles) en 100 ml de diclorometano se añadió trietilamina (3.23 ml, 23.16 mmoles) y se llevó hasta –50°C. Se añadió gota a gota una solución de anhídrido acético (1.459 ml, 15.44 mmoles) en 16 ml de diclorometano durante 45 min. La reacción se agitó a –50°C durante 30 min adicionales y después se regresó a temperatura ambiente. La reacción se verificó por UPLC/EM, que mostró los dos productos diaestereoméricos a 0.54 y 0.57 min, m/z = 328 (M+1). La mezcla de reacción se diluyó con diclorometano, se extrajo con $NaHCO_3$ saturado y salmuera, y se secó sobre Na_2SO_4. El crudo se purificó por cromatografía instantánea (sílice, CH_2Cl_2 →

CH_2Cl_2: NH_3 0.5 M en MeOH 90:10), obteniendo 4.334 g. 1H RMN (400 MHz, DMSO-d_6) indicó una mezcla de diaestereoisómeros con picos de diagnóstico a 0.05 ppm, y 0.03 ppm.

DESCRIPCION 41 y DESCRIPCION 42

***N*-[6-[(3*S*, 9a*R* o *S*)-8-acetil-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil) octahidro-2*H*-pirazino[1,2-a]pirazin-2-*il*]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (D41)-diaestereoisómero 1 y**

***N*-[6-[(3*S*, 9a*S* o *R*)-8-acetil-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil) octahidro-2*H*-pirazino[1,2-a]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (D42)-diaestereoisómero 2**



A una solución de (7*S*, 9a*R*)-2-acetil-7-({[(1,1-dimetiletil)(dimetil) silil]oxi}metil)octahidro-2*H*-pirazino[1,2-a]pirazina y (7*S*, 9a*S*)-2-acetil-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-2*H*-pirazino[1,2-a]pirazina (D40) (1.5 g, 5.72 mmoles) en 20 ml de tolueno se añadió 2-[3,5-bis(trifluorometil)fenil]-*N*-

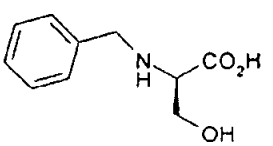
[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (2.034 g, 3.816 mmoles), bis-tri-ter-butilfosfinopaladio (440 mg, 0.86 mmoles), cloruro de hexadeciltrimetilamonio (73 µl de una solución acuosa al 25%) y, por último, solución de hidróxido de sodio (456 µl de una solución acuosa al 50%). La solución se desgasificó mediante dos ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C durante 4 hr. Se añadió más bis-tri-ter-butilfosfinopaladio (187 mg, 0.37 mmoles) y la reacción se agitó a 90°C durante 4 hr adicionales. La reacción se verificó por UPLC/EM, que mostró picos para losproductos esperados a 0.93 y 1.17 min, m/z = 824 (M+1) para ambos. La solución se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado, salmuera, y los compuestos orgánicos se secaron (Na_2SO_4). Los productos se aislaron por cromatografía instantánea (ciclohexano:EtOAc 70:30 → 0:100).

(D41) Diaestereoisómero 1, 1.1686 g, UPLC/EM: pico a 1.17 min, m/z = 824. M+1.

(D42) Diaestereoisómero 2, 1.0916 g, UPLC/EM: pico a 0.93 min, m/z = 824. M+1.

DESCRIPCION 43

N-(fenilmetil)-D-serina (D43)

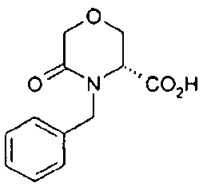


El compuesto del título se hizo de conformidad con el procedimiento descrito por G. R. Brown, J. Chem. Soc. Perkin Trans 1, 1985, 2577. Se añadió benzaldehído (10.16 ml, 0.1 moles) a una solución vigorosamente agitada de D-Serina (10.47 g, 0.1 moles) en solución de NaOH 2N (50 ml), se agitó durante 30 minutos a T.A. antes de que se enfriara en un baño de hielo con sal a ~6°C, y antes de añadir borhidruro de sodio (1.06 g, 27.90 mmoles) en porciones durante 40 minutos. La reacción se agitó a T.A. durante 1 hora, antes de que se añadiera más benzaldehído (10.16 ml, 0.1 moles) y de que se enfriara en un baño de hielo con sal entre 6-10°C, y después se añadió más borhidruro de sodio (1.06 g, 27.90 mmoles) en porciones durante 45 minutos. La mezcla de reacción se agitó a T.A. durante 2 horas, se lavó con Et_2O. Se aseguró todo el material sólido en solución, por lo tanto diluido con agua antes del lavado con Et_2O x2. La capa acuosa se acidificó a ~pH 6.5, usando solución de HCl concentrada. El sólido se precipitó. Se filtró, se secó en el horno de vacío durante la noche a 40°C para dar un sólido blanco en un rendimiento de 46%.

RMN (DMSO-d_6) δ 7.44-7.30 (5H, m), 3.98 (2H, q), 3.73-3.61 (1 H, m), 3.14 (1 H, m).

DESCRIPCION 44

Acido (3*R*)-5-oxo-4-(fenilmetil)-3-morfolincarboxílico



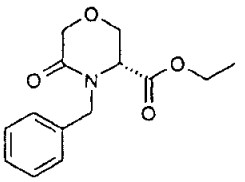
El compuesto del título se preparó de conformidad con el método descrito por H. H. Otto, Helvetica Chimica Acta, 2004, 87, 90. A una solución enfriada con hielo de N-(fenilmetil)-D-serina (8.90 g, 45.59 mmoles) en solución de NaOH 2N (50 ml) se añadió cloruro de cloroacetilo (4.36 ml, 54.71 mmoles), gota a gota durante 15 minutos. La reacción se agitó durante 30 minutos antes de añadir solución de NaOH al 30% (4.5 g en 15 ml) y agitando a T.A. durante 2 y ½ horas. Esta se enfrió en un baño de hielo antes de que se añadiera solución de HCl concentrada a pH < 1. El sólido se precipitó. Se filtró. Se suspendió en isopropanol y se calentó a reflujo durante 10 minutos. Se filtró caliente. El solvente se evaporó para dar un sólido amarillo pálido. Se trituró con Et_2O para dar el compuesto del título como un sólido color crema en un rendimiento de 29%.

EM (API+): m/z 236.1 (MH+: 100%) en un tiempo de retención de 1.61 min.

330

DESCRIPCION 45

(3*R*)-5-oxo-4-(fenilmetil)-3-morfolincarboxilato de etilo (D45)



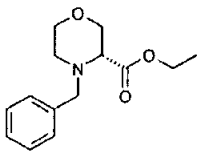
El compuesto del título se preparó de conformidad con el procedimiento descrito por H. H. Otto, Helvetica Chimica Acta, 2004, 87, 90 usando ácido (3*R*)-5-oxo-4-(fenilmetil)-3-morfolincarboxílico (D44, 3.13 g, 13.33 mmoles) en EtOH (30 ml), enfriando en un baño de hielo antes de añadir cloruro de tionilo (1.46 ml) gota a gota, y después agitando a T.A. durante 6 horas. Se añadió más cloruro de tionilo (1 ml) y se agitó a T.A. durante la noche. Se añadió más cloruro de tionilo (1 ml) y se agitó durante 4 horas, se añadió cloruro de tionilo adicional (0.5 ml) y se agitó nuevamente durante la noche. Se añadió cloruro de tionilo (0.2 ml) y se dejó agitar durante 5 horas. El solvente se evaporó para dar el compuesto del título como un aceite anaranjado en rendimiento cuantitativo.

EM (API+): m/z 264.1 (MH+; 100%) en un tiempo de retención de 2.28 min

$[\alpha]_D$ =-11.4°, en donde l = 1 cm, c = 0.5 en DCM

DESCRIPCION 46

(3*R*)-4-(fenilmetil)-3-morfolincarboxilato de etilo (D46)



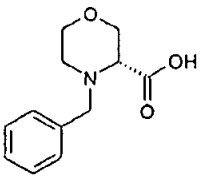
El compuesto del título se preparó de conformidad con el procedimiento usado por G. R. Brown, J. Chem. Soc. Perkin Trans 1, 1985, 2577, usando (3*R*)-5-oxo-4-(fenilmetil)-3-morfolincarboxilato de etilo (D45, 3.64 g, 13.84 mmoles) en THF seco (70 ml), enfriado en un baño de hielo antes de añadir lentamente complejo de borano-sulfato de dimetilo (1.84 ml, 10M). La mezcla de reacción se dejó calentar a temperatura ambiente durante la noche. Se agitó durante seis horas adicionales, se añadió más complejo de borano-sulfato de dimetilo y se agitó a T.A. durante el fin de semana. La reacción se extinguió cuidadosamente con agua, gota a gota hasta que la efervescencia se había terminado. El solvente se evaporó. El residuo se disolvió en agua, se basificó a pH ~10 usando solución de NaOH 2N antes de extraer con Et_2O. La capa orgánica después se extrajo con solución de HCl 2N. La capa ácida se basificó después usando solución de NaOH 2N antes de extraer con Et_2O x 3. Los extractos combinados se secaron ($MgSO_4$). Se filtraron. Se evaporaron bajo presión reducida para dar el compuesto del título como un aceite incoloro en un rendimiento de 68%.

EM (API+): m/z 250.1 (MH+: 100%) en un tiempo de retención de 1.88 min

$[\alpha]_D$ = + 103°, en donde l = 1 cm, c = 0.5 en DCM

DESCRIPCION 47

Acido (3*R*)-4-(fenilmetil)-3-morfolincarboxílico (D47)



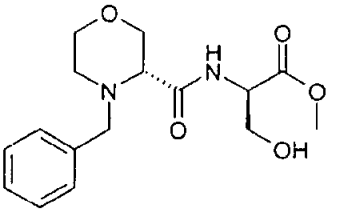
(3*R*)-4-(fenilmetil)-3-morfolincarboxilato de etilo (D46, 2.33 g, 9.36 mmoles) se disolvió en una mezcla de THF/EtOH/H_2O (1:1:1 45 ml) antes de que se tratara con hidróxido de litio monohidratado (0.432 g, 10.29 mmoles) y se calentara a 50°C durante la noche. La reacción no se terminó. Se añadió más hidróxido de litio monohidratado (0.200 g, 4.76 mmoles) y se dejó calentar durante 24 horas adicionales. Se añadió más hidróxido de litio (0.100 g, 2.38 mmoles) y se calentó durante 6 horas adicionales. Se añadió más hidróxido de litio (0.100 g, 2.38 mmoles) y se calentó durante 16 horas adicionales. Se enfrió a T.A. La reacción se neutralizó usando solución de HCl 2N. El solvente se evaporó. El residuo se dividió entre DCM y agua. La capa acuosa se extrajo con 10% de MeOH/DCM x5. Los extractos combinados se secaron ($MgSO_4$). Se filtraron. El solvente se evaporó bajo presión reducida para dar el compuesto del título como una espuma blanca en un 94% de rendimiento.

EM (API+): m/z 222.1 (MH+; 100%) en un tiempo de retención de 0.96 min

$[\alpha]_D$ = + 73°, en donde l = 1 cm, c = 0.5 en MeOH

DESCRIPCION 48

N-{[(3*R*)-4-(fenilmetil)-3-morfolinil]carbonil}-D-serinato de metilo (D48)



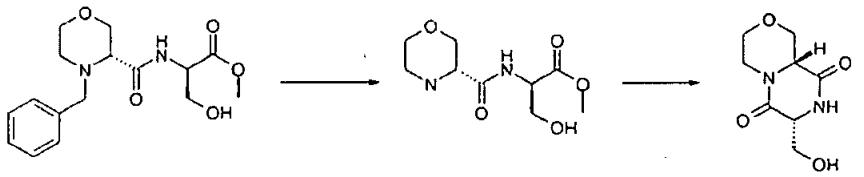
Acido (3*R*)-4-(fenilmetil)-3-morfolincarboxílico (D47, 1.93 g, 8.73 mmoles) se disolvió en DCM seco (20 ml) con un poco de DMF (2 ml). A ésta se añadió TBTU (3.62 g, 11.27 mmoles) seguido por DIPEA (3.02 ml, 17.29 mmoles) y se agitó durante 40 minutos a T.A., bajo argón antes de añadir una solución de clorhidrato de éster D-Ser-metílico (2.70 g, 17.37 mmoles), y DIPEA (3.02 ml, 17.29 mmoles) en DCM seco (15 ml). La mezcla resultante se agitó durante 45 minutos antes de dejarse reposar durante la noche. Diluido con DCM (60 ml), se lavó con solución de $NaHCO_3$ saturada (2 x 60 ml). Se secó (Na_2SO_4). Se filtró. El solvente se evaporó bajo presión reducida para dar un aceite anaranjado. Se usó crudo en el siguiente paso.

EM (API+): m/z 323.1 (MH+; 100%) en un tiempo de retención de 1.17 min

$[\alpha]_D$ = + 11.8 °, en donde l = 1 cm, c =0.5 en DCM

DESCRIPCION 49

(7*S*,9a*S*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol (D49)



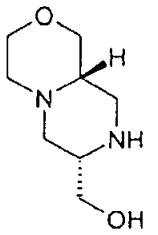
N-{[(3R)-4-(fenilmetil)-3-morfolinil]carbonil}-D-serinato de metilo (D48, 3.72 g, 11.55 mmoles) se disolvió en EtOH (50 ml), se trató con 10% de Pd sobre C (450 mg) después se colocó bajo una atmósfera de hidrógeno durante el fin de semana. Se dejó agitando durante 6 horas adicionales. Se añadió 10% de Pd sobre C (200 mg) y se dejó bajo una atmósfera de hidrógeno durante la noche. El catalizador se removió por filtración a través de un filtro de Kieselguhr lavado con ácido, lavando bien con EtOH. El solvente se removió bajo presión reducida para dar un aceite incoloro. El aceite se disolvió en MeOH seco (15 ml) y se calentó a 50°C durante la noche. Se dejó calentar durante 3 horas adicionales antes de enfriarse a T.A. El solvente se removió bajo presión reducida. El residuo se trituró con DCM para dar el compuesto del título como un sólido blanquecino en un rendimiento de 35% durante en los 2 pasos.

EM (ELSD+): 201.1 (MH+; 100%) en un tiempo de retención de 0.49 min

$[\alpha]_D$ = + 37.6 °, en donde l = 1 cm, c = 0.5 en MeOH

DESCRIPCION 50

(7*S*,9a*S*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol (D50)



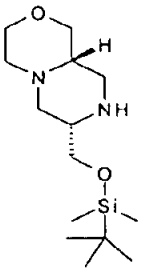
(7*S*,9a*S*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol (D49, 800 mg, 4 mmoles) se suspendió en THF seco (20 ml), antes de ser tratado con solución de complejo de borano-THF 1 M (40 ml) y calentarse a reflujo durante 17 horas. Se enfrió a T.A., se añadió gota a gota MeOH (8 ml) seguido por solución de HCl concentrada (3.2 ml). La mezcla resultante se calentó a 70°C durante 2 horas. Se enfrió a T.A., el solventee se evaporó bajo presión reducida. El residuo se colocó sobre una columna SCX de 10g en MeOH con algo de agua. La columna se lavó con MeOH (3x 25 ml) antes de eluir el compuesto con NH_3 en MeOH (4 x 25 ml). El solvente se evaporó bajo presión reducida para dar el compuesto del título como un aceite incoloro en un rendimiento cuantitativo.

EM (ELSD+): m/z 173.1 (MH+; 100%) en un tiempo de retención de 0.31 min

$[\alpha]_D$ = + 3.6°, en donde l = 1 cm, c = 0.5 en MeOH

DESCRIPCION 51

(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D51)



(7*S*,9a*S*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol (D50, 680 mg, 3.95 mmoles) casi se disolvió en DCM seco (12 ml) antes de añadir Et3N (1.10 ml, 7.90 mmoles), seguido por cloruro de TBDMS (894 mg, 5.93 mmoles). La mezcla de reacción resultante se agitó durante el fin de semana a T.A., bajo argón. Se dejó agitar durante 2 horas más.

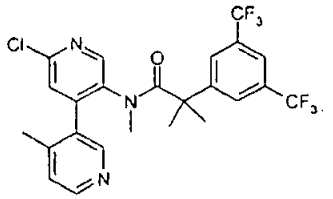
Se diluyó con DCM, se lavó con solución de $NaHCO_3$ saturada (2 x 20 ml). Se secó ($MgSO_4$). Se filtró. El solvente se evaporó. El residuo se purificó sobre una columna horizontal 25 + M eluyendo con 10% de EtOAc/Éter de pet. a EtOAc a 10% de MeOH/EtOAc. El solvente se evaporó bajo presión reducida para dar el compuesto del título como un aceite amarillo pálido en un rendimiento de 62%.

^{1}H RMN (400MHz; DMSO-d_6) δ 3.77-3.63 (3H, m), 3.50-3.40 (2H, m), 2.98 (1 H, t), 2.71 (1 H, br m), 2.61 (1H, dd), 2.42-2.28 (4H, m), 2.14-2.05 (2H, m), 1.96 (1 H, m), 0.83 (9H, s), 0.01 (6H, s)

$[\alpha]_D$ = + 4.4°, en donde l = 1 cm, c = 0.5 en DCM

DESCRIPCION 52

2-[3,5-bis(trifluorometil)fenil]-*N*-(6'-cloro-4-metil-3,4'-bipiridin-3'-il)-*N*,2-dimetilpropanamida (D52)



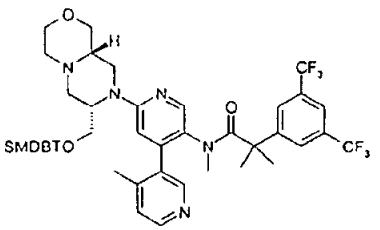
2-[3,5-bis(trifluorometil)fenil]-*N*-(6-cloro-4-yodo-3-piridinil)-*N*,2-dimetilpropanamida (400 mg, 0.726 mmoles), ácido 4-metilpiridin-3 borónico (130 mg, 0.944 mmoles), carbonato de sodio (0.8 ml, 2M), tetrakistrifenilfosfin-paladio (7.8 mg, 0.00726 mmoles) se añadió en dioxano (4 ml) y se agitó bajo argón antes de calentarse en el microondas a 110°C durante 30 minutos, se añadió más ácido 4-metilpiridin-3-borónico (67.5 mg, 0.49 mmoles) y tetrakistrifenilfosfinpaladio (7.8 mg, 0.00726 mmoles) y se calentó a 110°C durante 30 minutos, posteriormente se añadió más ácido 4-metilpiridin-3 borónico (51 mg, 037 mmoles), tetrakistrifenilfosfinpaladio (7.8 mg, 0.00726 mmoles) y se calentó bajo condiciones de microondas a 110°C durante 30 minutos, posteriormente se añadió ácido 4-metilpiridin-3-borónico (47 mg, 0.34 mmoles), tetrakistrifenilfosfinpaladio (7.8 mg, 0.00726 mmoles) y se calentó a 110°C durante 30 minutos. El residuo se dividió entre EtOAc y salmuera. La capa acuosa se extrajo con EtOAc x3. Los extractos combinados se secaron y el solvente se evaporó. El residuo se purificó sobre una columna horizontal 12 + M eluyendo con eter de pet. a 1:1 de EtOAc:éter de pet. No se pudieron

aislar fracciones limpias. La muestra se envió para ser purificada por cromatografía Auto-Prep dirigida a la masa (MDAP), se encontró que el sólido blanco que no se disolvió era el material deseable. Este se combinó con el producto aislado a partir de la MDAP para dar el compuesto del título como un sólido blanco en un rendimiento de 83%.

EM (API+): m/z 516.1 (MH+; 100%)

DESCRIPCION 53

2-[3,5-bis(Trifluorometil)fenil]-N-{6'-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1H)-il]-4-metil-3,4'-bipiridin-3'-il}-N,2-dimetilpropanamida (D53)



La 2-[3,5-bis(trifluorometil)fenil]-*N*-(6'-cloro-4-metil-3,4'-bipiridin-3'-il)-*N*,2-dimetilpropanamida (D52, 77 mg, 0.15 mmoles), (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D51, 51.5 mg, 0.18 mmoles), t-butóxido de sodio (18 mg, 0.19 mmoles) se desgasificaron juntos en tolueno seco (1.5 ml) durante 5 minutos antes de añadir Bis(dibencilenacetona) paladio (9 mg, 0.015 mmoles) y 2-diciclohexilfosfino-2'-(N'N'-dimetilamino)bifenilo (15 mg, 0.038 mmoles) y se calentaron bajo condiciones de microondas a 130°C durante 30 mins. Se

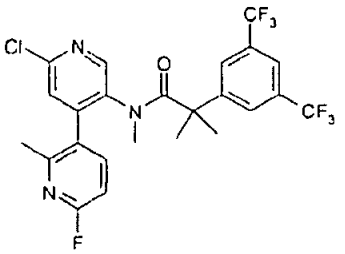
diluyeron con EtOAC, se lavaron con $NaHCO_3$ saturado x1 , salmuera x1, se secaron ($MgSO_4$). Se filtraron. El solvente se evaporó. El residuo se purificó eluyendo con Pent a EtOAc. Las fracciones no se aislaron limpias. Las fracciones mixtas se combinaron, el solvente se evaporó y residuo se volvió a purificar sobre una columna de SCX 2g, lavando con MeOH (2x10 ml) antes de eluir el compuesto con NH_3 en MeOH (3x10 ml). El solvente se evaporó bajo presión reducida para dar un sólido gomoso (86 mg).

EM (API+: 766.4 (MH+;100%) + 652.2 (MH+; -TBDMS ; 20%)

El producto crudo se usó directamente sin purificación adicional.

DESCRIPCION 54

2-[3,5-bis(trifluorometil)fenil]-*N*-(6'-cloro-6-fluoro-2-metil-3,4'-bipiridin-3'-il)-*N*,2-dimetilpropanamida (D54)



2-[3,5-bis(trifluorometil)fenil]-*N*-(6-cloro-4-yodo-3-piridinil)-*N*,2-dimetilpropanamida (200 mg, 0.363 mmoles), ácido 2-fluoro-6-metilpiperidin-5 borónico (73 mg, 0.472 mmoles), solución de carbonato de sodio (0.4 ml, 2M), tetrakistrifenilfosfinpaladio (4 mg, 0.00363 mmoles) en dioxano (2 ml) se calentaron juntos en el microondas a 110°C durante 30 minutos. La mezcla se

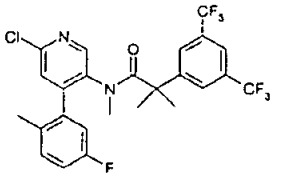
dividió entre EtOAc y solución de $NaHCO_3$ saturada. La capa acuosa se extrajo con EtOAc x3. Los extractos combinados se secaron y se evaporaron. El residuo se purificó sobre un columna horizontal 12+M eluyendo con Pet Et_2O a 60% de EtOAc/Pet Et_2O. El solvente se evaporó bajo presión reducida para dar el compuesto del título en rendimiento cuantitativo.

340

EM (API+): m/z 534.2 (MH+; 100%)

DESCRIPCION 55

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(5-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D55)

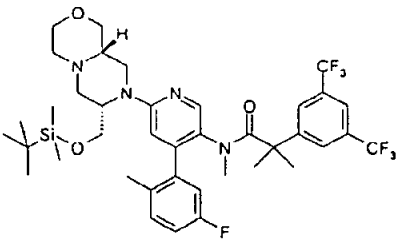


2-[3,5-bis(trifluorometil)fenil]-*N*-(6-cloro-4-yodo-3-piridinil)-*N*,2-dimetilpropanamida (200 mg, 0.363 mmoles), ácido 2-metil-5-fluorobencenborónico (73 mg, 0.472 mmoles), carbonato de sodio (0.4 ml, solución 2M), tetrakistrifenilfosfinpaladio (4 mg, 0.00363 mmoles) en dioxano se calentaron juntos en el microondas a 110°C durante 30 minutos. La mezcla se dividió entre EtOAc y salmuera. La capa acuosa se extrajo con EtOAc x3. Los extractos combinados se secaron y se evaporaron. El residuo se purificó sobre una columna 12+M eluyendo con Pet Et_2O a 60% de EtOAc/ Pet Et_2O para dar el compuesto del título en un rendimiento de 27%.

EM (API+): m/z 533.1 (MH+; 100%)

DESCRIPCION 56

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(5-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D56)

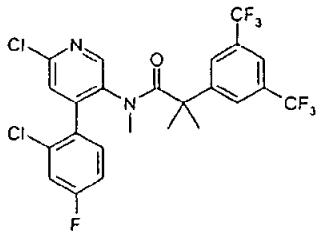


2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(5-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D55, 50 mg, 0.094 mmoles), (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D51, 34 mg, 0.116 mmoles) se disolvieron en tolueno (1.5 ml). Se añadieron Bis tritertbutilfosfin-paladio (12.5 mg, 0.0244 mmoles), seguido por cloruro de hexadeciltrimetilamonio (20 µl, solución acuosa al 25%), y finalmente solución de hidróxido de sodio (0.11 ml, solución acuosa al 50%). La mezcla se desgasificó durante 5 minutos antes de que se calentara a 90°C durante 2 horas. La reacción se enfrió a T.A., se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ saturada, se secó ($MgSO_4$). Se filtró. El solvente se evaporó para dar un sólido pegajoso amarillo. Se usó crudo en el siguiente paso.

EM (API+): 783.4 (MH+; 60%)

DESCRIPCION 57

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-cloro-4-fluorofenil)-3-piridinil]-*N*,2-dimetilpropanamida (D57)

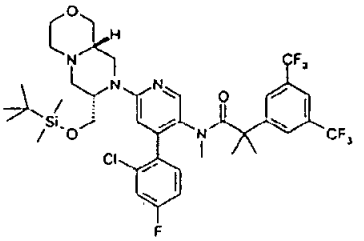


2-[3,5-bis(trifluorometil)fenil]-*N*-(6-cloro-4-yodo-3-piridinil)-N,2-dimetilpropanamida (200 mg, 0.363 mmoles), ácido 2-cloro-4-fluorobencenborónico (82 mg, 0.472 mmoles), carbonato de sodio (0.4 ml, solución 2M), tetrakistrifenilfosfinpaladio (4 mg, 0.00363 mmoles) en dioxano (2 ml) se calentaron juntos en el microondas a 110°C durante 30 minutos. La mezcla se dividió entre EtOAc y salmuera. La capa acuosa se extrajo con EtOAc x3. Los extractos combinados se secaron y se evaporaron. El residuo se purificó sobre una columna 25+M eluyendo con 0-50% de EtOAc/Pet Et_2O. Las impurezas todavía se veían. Se envió a MDAP para purificación para dar el compuesto del título en un rendimiento de 96%.

EM (API+): m/z 553.1 (MH+; 100%)

DESCRIPCION 58

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(2-cloro-4-fluorofenil)-6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (D58)

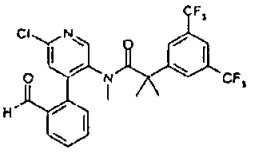


2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-cloro-4-fluorofenil)-3-piridinil]-*N*,2-dimetilpropanamida (D57, 60 mg, 0.11 mmoles), (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D51, 37 mg, 0.13 mmoles), t-butóxido de sodio (13 mg, 00.1375 mmoles) se desgasificaron juntos en tolueno (1.2 ml) durante 10 minutos antes de añadir bis(dibencilenacetona)paladio (6 mg, 0.011 mmoles) y 2-diciclohexilfosfin-2'-(N,N-dimetilamino)bifenilo (11 mg, 0.0275 mmoles) y calentando a 100°C durante 30 minutos bajo condiciones de microondas. Se añadió más bis(dibencilenacetona)paladio (6 mg, 0.011 mmoles) y 2-diciclohexilfosfino-2'-(N,N-dimetilamino)bifenilo (11 mg, 0.0275 mmoles) y se calentó durante 30 minutos adicionales a 100°C bajo condiciones de microondas. Se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ saturada x1, salmuera x1, se secó ($MgSO_4$). Se filtró. El solvente se evaporó bajo presión reducida. El residuo se purificó eluyendo con 0-100% de EtOAc/Pent. El solvente se evaporó para dar una goma café del compuesto del título en un rendimiento de 25%.

EM (API+): m/z 803.4 (MH+; 40%)

DESCRIPCION 59

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-formilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D59)

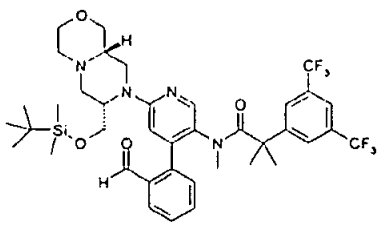


2-[3,5-bis(trifluorometil)fenil]-*N*-(6-cloro-4-yodo-3-piridinil)-*N*,2-dimetilpropanamida (200 mg, 0.363 mmoles), ácido benzaldehído-2-borónico (71 mg, 0.472 mmoles), carbonato de sodio (0.4 ml, solución 2M), tetrakistrifenilfosfinpaladio (4 mg, 0.00363 mmoles) en dioxano (2 ml) se calentaron juntos en el microondas a 110°C durante 30 minutos. La mezcla se dividió entre EtOAc y salmuera. La capa acuosa se extrajo con EtOAc x3. Los extractos combinados se secaron y se evaporaron. El residuo se purificó sobre una columna 25+M eluyendo con 0-50% de EtOAc/ Pet Et_2O para dar el compuesto del título como un sólido amarillo en un rendimiento de 55%.

EM (API+): m/z 529.1 (MH+; 100%)

DESCRIPCION 60

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(2-formilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D60)

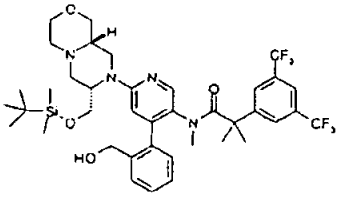


2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-formilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D59, 106 mg, 0.201 mmoles), (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D51, 72 mg, 0.251 mmoles) se disolvieron en tolueno (2 ml). Se añadieron bis tritertbutilfosfinpaladio (27 mg, 0.052 mmoles), seguido por cloruro de hexadeciltrimetilamonio (30 µl, solución acuosa al 25%), y finalmente solución de hidróxido de sodio (0.25 ml, solución acuosa al 50%). La mezcla se desgasificó durante 5 minutos antes de calentarse a 90°C durante 2 horas. la reacción se enfrió a T.A., se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ saturada, se secó ($MgSO_4$). Se filtró. El solvente se evaporó. El residuo se purificó eluyendo con 0-50% de EtOAc/Pent. El solvente se evaporó bajo presión reducida para dar un sólido amarillo pálido en un rendimiento de 18%.

EM (API+): m/z 779.4 (MH+; 100%).

DESCRIPCION 61

2-[3,5-bis(trifluorometil)fenil]-*N*-{6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-[2-(hidroximetil)fenil]-3-piridinil}-*N*,2-dimetilpropanamida (D61)

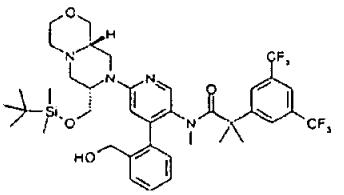


2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazin[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(2-formilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D60, 27.7 mg, 0.0356 mmoles) se suspendió en THF seco (1.5 ml) antes de añadir borhidruro de sodio (3 mg, 0.078 mmoles) y agitando durante 1 hora. Se añadió más borhidruro de sodio (3 mg, 0.078 mmoles) y se dejó agitando durante 1 ½ horas adicionales. La reacción se extinguió con agua, se diluyó con EtOAc. La capa orgánica se lavó con agua, se secó ($MgSO_4$). Se filtró. El solvente se evaporó para dar el compuesto del título como un sólido blanquecino en un rendimiento de 89%. Se usó crudo en el siguiente paso.

EM (API+): m/z 781.4 (MH+; 100%).

DESCRIPCION 62

2-[3,5-bis(trifluorometil)fenil]-*N*-(4-(4-fluoro-2-metilfenil)-6-{[(2*S*)-2-pirrolidinilmetil]amino}-3-piridinil)-*N*,2-dimetilpropanamida (D62)

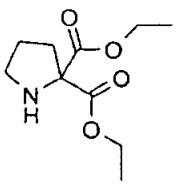


Una suspensión de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (1.5 g, 2.81 mmoles) (2*R*)-2-(aminometil)-1-pirrolidincarboxilato de 1,1-dimetiletilo (N-Boc prolinamina) (1.41 g, 7.025 mmoles) y carbonato de potasio (777 mg, 5.62 mmoles) en 6 ml de DMSO se calentó durante 18 hr a 150°C (temperatura detectada 138°C). Una verificación de CLAR/EM mostró una conversión al 50% con pérdida parcial del grupo protector Boc. La reacción se calentó bajo irradiación de microondas a 160°C durante 1 hr y a 180°C durante dos ciclos de 1 hr y 1.5 hr, respectivamente. La suspensión se diluyó con diclorometano y se extrajo con $NaHCO_3$ saturado y los compuestos orgánicos se secaron (Na_2SO_4) y la solución se cargó sobre un cartucho de SCX, se lavó con diclorometano (100 ml) y metanol (200 ml, este lavado permitió la recuperación de la cloropiridina sin reaccionar) y se eluyó con NH_3 2M en MeOH. El crudo así obtenido obtenido, que contenía tanto los compuestos Boc-protegidos y no protegidos, se purificó por cromatografía instantánea (sílice, ciclohexano: EtOAc 80:20 a EtOAc). Se aislaron 350 mg

de Boc-amina protegida y 410 mg del compuesto del título. Este último compuesto se purificó adicionalmente mediante una protección boc, cromatografía instantánea, desprotección de TFA y procedimiento de aislamiento SCX. Rendimiento final: 165 mg. O.A.CLAR, pico en 5.20 min, > 99% de pureza (UV).

DESCRIPCION 63

2,2-Pirrolidindicarboxilato de dietilo (D63)



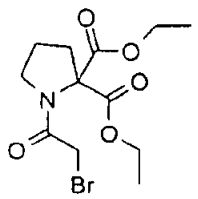
A una solución de etóxido de sodio (5.14 g) en etanol absoluto (75 ml) a 0°C bajo una atmósfera de nitrógeno, se añadió lentamente una solución de aminomalonato de dietilo (sal de clorhidrato, 8 g) en etanol absoluto (75 ml). Una suspensión amarilla se obtuvo al final de la adición. 1,3-dibromopropano (7.7 ml) después se añadió y la mezcla resultante se agitó a temperatura de reflujo durante 5 horas. La mezcla se dejó enfriar a t.a., después se removió el etanol bajo vacío para dar un sólido amarillo. Este se disolvió en HCl (solución 1M, 20 ml) y después se lavó con éter etílico (2 x 50 ml). Las fases se separaron y la fase acuosa se llevó a pH = 9 mediante la adición de NaOH (solución 1M). Después se extrajo con éter etílico (3 x 50 ml) y se lavó con salmuera (20 ml). La fase orgánica se secó y se concentró bajo

vacío para dar el compuesto deseado (2.35 g) como aceite amarillo.

EM (ES/+) m/z=216 $[M+H]^+$.

DESCRIPCION 64

1-(Bromoacetil)-2,2-pirrolidindicarboxilato de dietilo (D64)



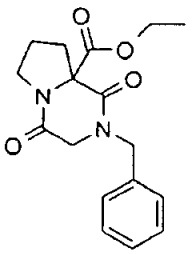
A una solución de 2,2-pirrolidindicarboxilato de dietilo (D63, 900 mg) en diclorometano (9 ml) a 0°C, se añadieron carbonato de potasio (solución 0.5M, 12.5 ml) y bromuro de bromoacetilo (0.55 ml). La mezcla resultante se agitó a 0°C durante 2 horas. La mezcla después se diluyó con agua y después se dejó que alcanzara la t.a. Se añadió acetato de etilo (15 ml) y las fases se separaron. La fase acuosa se extrajo después con acetato de etilo (2 x 10 ml) y se lavó con salmuera (20 ml). La fase orgánica se secó y se concentró bajo vacío para dar el compuesto deseado (1.06 g) como aceite anaranjado.

CCD: CH/AcOEt 1:1, Rf = 0.47.

UPLC/EM: pico a Tr = 0.63 min con m/z = 336, 338 $[M+H]^+$.

DESCRIPCION 65

1,4-Dioxo-2-(fenilmetil)hexahidropirrolo[1,2-*a*]pirazina-8a(6*H*)-carboxilato de etilo (D65)



A una solución de 1-(bromoacetil)-2,2-pirrolidindicarboxilato de dietilo (D64, 950 mg) en acetonitrilo (10 ml) a t.a., se añadió bencilamina (340 microlitros). La mezcla resultante se agitó a t.a. durante 3.5 horas: se observó la formación de un sólido blanco. La suspensión después se filtró sobre un embudo de Gooch. El filtrado orgánico se diluyó con acetato de etilo (15 ml) y se lavó con agua (2 x 10 ml). La fase orgánica se secó y se concentró bajo vacío a un residuo que se purificó por cromatografía instantánea (Cycl/EtOAc de 50/50 a 35:65) para dar el compuesto deseado (200 mg) como aceite incoloro.

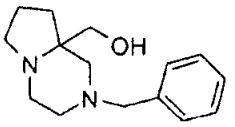
CCD: CH/AcOEt 7:3, Rf=0.53.

UPLC/EM: pico a Tr = 0.62 min con m/z = 317 $[M+H]^+$.

^{1}H RMN (500 MHz, CLOROFORMO-*d*) d ppm 7.34 (t, 1H) 7.32 (t, 2H) 7.23 (dd, 2H) 4.97 (d, 1H) 4.25 (d, 1H) 4.19-4.25 (m, 2H) 4.01 (d, 1H) 3.74 (d, 1H) 3.67-3.76 (m, 1H) 3.55-3.63 (m, 1H) 2.71-2.80 (m, 1H) 2.36-2.46 (m, 1H) 1.93-2.11 (m, 2H) 1.21 (t, 3 H).

DESCRIPCION 66

[2-(Fenilmetil)hexahidropirrolo[1,2-*a*]pirazin-8a(6*H*)-il]metanol (D66)



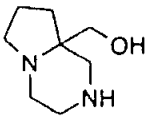
A una solución de 1,4-dioxo-2-(fenilmetil)hexahidropirrolo[1,2-*a*]pirazina-8a(6*H*)-carboxilato de etilo (D65, 450 mg) en THF anhidro (5 ml) bajo una atmósfera de nitrógeno a 0°C, se añadió gota a gota hidruro de litio-aluminio (1 M en THF, 14 ml). La mezcla resultante se agitó a 0°C durante 10 minutos, después se dejó que alcanzara t.a. y se agitó a esta temperatura durante 45 minutos. Después se calentó a temperatura de reflujo durante 3.5 horas y después se dejó enfriar a t.a. Después se añadieron agua (540 microlitros), NaOH (solución 1M, 540 microlitros) y agua (1.6 ml) a la solución y se observó la formación de un precipitado blanco. La suspensión se agitó a t.a. durante 30-40 minutos, después se filtró sobre un embudo de Gooch. El filtrado orgánico se secó y se concentró bajo vacío a un residuo que se purificó por cromatografía instantánea (DCM/MeOH a partir de 100/0 a 90:10) para dar el compuesto deseado (162 mg) como aceite anaranjado.

CCD: DCM/MeOH 9:1 , Rf=0.43.

UPLC/EM: pico a Tr = 0.43 min con m/z = 247 $[M+H]^+$.

DESCRIPCION 67

Hexahidropirrolo[1,2-*a*]pirazin-8a(6*H*)-ilmetanol (D67)



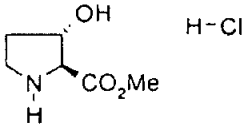
A una solución de [2-(fenilmetil)hexahidropirrolo[1,2-*a*]pirazin-8a(6*H*)-il]metanol (D66, 180 mg) en metanol anhidro (5 ml) bajo una atmósfera de nitrógeno a t.a., se añadieron formiato de amonio (475 mg) y paladio (10% sobre carbón, 13 mg). La suspensión resultante se calentó a temperatura de reflujo durante 3.5 horas, después se dejó enfriar a r.t. y se filtró sobre Celite. El extracto orgánico se secó y se concentró bajo vacío para dar el compuesto deseado (120 mg) como un sólido ceroso anaranjado.

UPLC/EM: pico a Tr = 0.15 min con m/z = 157 $[M+H]^+$.

^{1}H RMN (400 MHz, DMSO-d_6) d ppm 5.09 (br. s., 1H) 3.61 (d, 1H) 3.34 (br. s., 1H) 2.89-3.09 (m, 5 H) 2.76-2.89 (m, 2H) 2.72 (d, 1H) 1.62-1.84 (m, 3 H) 1.49-1.61 (m, 1H)

DESCRIPCION 68

Clorhidrato de (3*S*)-3-hidroxi-L-prolinato de metilo (D68)



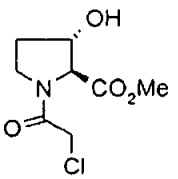
Cloruro de hidrógeno gaseoso se hizo burbujear a través de una

suspensión de *trans*-3-hidroxi-L-prolina (1.5 g, 11.4 mmoles) en 20 ml de MeOH recién destilado a 0°C durante 30 min. La solución clara resultante se agitó durante la noche, después se concentró bajo presión reducida para dar el compuesto del título como un sólido blanco (1.96 g). Rendimiento de 94%.

Referencia: Solicitud de patente de E.U.A. 2004 19,063.

DESCRIPCION 69

(3*S*)-1-(cloroacetil)-3-hidroxi-L-prolinato de metilo (D69)

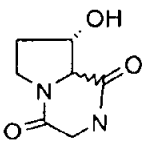


A una solución del clorhidrato de (3*S*)-3-hidroxi-L-prolinato de metilo (D68, 1.8 g, 9.9 mmoles) y Et_3N (3 ml, 21.8 mmoles) en 10 ml de benceno seco a temperatura DE 7-8°C se añadió gota a gota una solución de cloruro de cloroacetilo (0.87 ml, 10.9 mmoles) en 5 ml de benceno seco. Después de 24 hr a t.a., el precipitado se filtró y se lavó con AcOEt. El filtrado se evaporó, y el aceite crudo se purificó por cromatografía en columna instantánea (Cy/AcOEt 1/4 como eluyente). El compuesto del título se aisló como un aceite incoloro (1.48 g). Rendimiento 67%.

Referencia: *Khimiko-Farmatsevticheskii Zhurnal* 1984, 18, 1445-8; *Eur. J. Org. Chem.* 2000, 657.

DESCRIPCION 70

(8*S*)-8-hidroxihexahidropirrolo[1,2-*a*]pirazina-1,4-diona (D70)

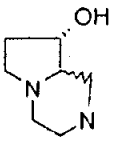


Una mezcla de (3*S*)-1-(cloroacetil)-3-hidroxi-L-prolinato de metilo (D69, 1.48 g, 6.7 mmoles) en 10 ml de MeOH y 60 ml de una solución saturada de NH_3 en MeOH se agitó durante 48 hr a t.a.. El solvente se evaporó bajo presión reducida, para dar un sólido. El análisis indicó que esto era el compuesto del título como un par de diaestereoisómeros. Después de una cromatografía en columna corta ($CHCl_3$/MeOH 8/2 como eluyente) el compuesto del título se aisló como un sólido espumoso (1 g). Rendimiento 88%.

Referencia: *Khimiko-Farmatsevticheskii Zhurnal* 1984, 18, 1445-8

DESCRIPCION 71

(8*S*)-octahidropirrolo[1,2-*a*]pirazin-8-ol (D71)



En una suspensión agitada, enfriada (0 °C) de $LiAlH_4$ (3.3 g, 88 mmoles) en 60 ml de THF seco, se introdujo (8*S*)-8-hidroxihexahidropirrolo[1,2-*a*]pirazina-1,4-diona (D70, 750 mg, 4.4 mmoles) en

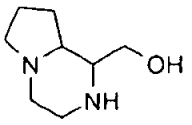
porciones pequeñas. La mezcla después se dejó que alcanzara t.a. y se agitó durante 48 hr, después de lo cual se enfrió a 0°C. Se introdujo THF (70 ml), después sucesivamente una solución saturada de Na-K-tartrato (5 ml) y una solucion de NaOH acuosa al 20% (5 ml) se hicieron gotear en el matraz, bajo agitación vigorosa. La suspensión se agitó durante 30 min a t.a., y se filtró. La torta de filtro pálida se lavó con 100 ml de $CHCl_3$ y los filtrados y lavados combinados se evaporaron bajo vacío para dar 500 mg del compuesto del título. A partir del análisis de CG-EM, aún se observaron 2 productos diaestereoméricos. Rendimiento 80%.

^{1}H RMN (500 MHz, DMSO-*d6*) δ ppm 4.01 (s, 1H) 2.93 (t, 1H) 2.87 (d, 1H) 2.80 (d, 1H) 2.71 (d, 1H) 2.49-2.61 (m, 2H) 1.89-2.06 (m, 2H) 1.74-1.91 (m, 2H) 1.48-1.56 (m, 1H) 1.34-1.42 (m, 1H)

Referencia: *J. Org. Chem.* 1995, 60, 3916.

DESCRIPCION 72

cis-Octahidropirrolo[1,2-*a*]pirazin-1-ilmetanol (D72)



A una solución de 3-oxooctahidropirrolo[1,2-*a*]pirazin-1-carboxilato de *cis*-metilo (Preparada de conformidad con los procedimientos de la literatura: Heterocycles, 52(3), 2000 (270 mg) en THF anhidro (10 ml) bajo una atmósfera de nitrógeno a 0°C, se añadió gota a gota hidruro de litio-

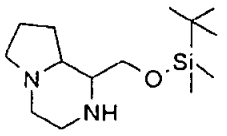
aluminio (1 M en THF, 6.8 ml). La mezcla resultante se agitó a 0°C durante 1 hora, después se dejó que alcanzara t.a. y se agitó a esta temperatura durante 30 minutos. Después se añadieron agua (260 microlitros), NaOH (solución 1M, 260 microlitros) y agua (780 microlitros) a la solución y se observó la formación de un precipitado blanco. La suspensión se filtró sobre un embudo de Gooch. El filtrado orgánico se secó y se concentró bajo vacío para dar el compuesto deseado (198 mg) como aceite amarillo.

UPLC/EM: pico a Tr = 0.15 min con m/z = 157 $[M+H]^+$.

^{1}H RMN (500 MHz, CLOROFORMO-*d*) d ppm 3.94-4.04 (m, 1H) 3.75 (dd, 1H) 3.19 (td, 1H) 3.07-3.15 (m, 1H) 3.05 (t, 1H) 2.96-3.04 (m, 1H) 2.78-2.90 (m, 2H) 2.29-2.40 (m, 1H) 2.17 (td, 1H) 2.02-2.15 (m, 1H) 1.58-1.86 (m, 4 H).

DESCRIPCION 73

cis-1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirrolo[1,2-*a*] pirazina (D73)



A una solución de cis-Octahidropirrolo[1,2-a]pirazin-1-ilmetanol (D72, 198 mg) en DCM anhidro (10 ml) bajo una atmósfera de nitrógeno a temperatura ambiente, se añadieron trietilamina (350 microlitros) y cloruro de t-butildimetilsililo (286 mg). La solución resultante se agitó a temperatura

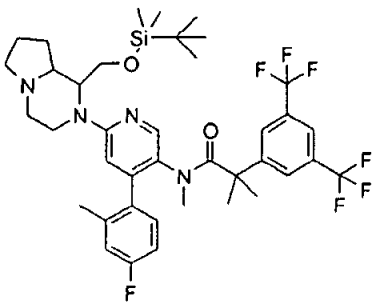
ambiente durante la noche, después se diluyó con agua (5 ml). La fase acuosa se extrajo con DCM (2 x 10 ml). Los extractos orgánicos combinados se secaron y se concentraron bajo vacío a un residuo que se purificó por cromatografía instantánea (DCM/NH_3 0.5M en MeOH a partir de 100/0 a 90/10) para dar el compuesto deseado (195 mg) como aceite amarillo.

UPLC/EM: pico a Tr = 0.80 min con m/z = 271 $[M+H]^+$.

^{1}H RMN (500 MHz, CLOROFORMO-*d*) d ppm 3.84 (t, 1H) 3.61 (dd, 1H) 3.11-3.21 (m, 1H) 2.99 (dd, 2H) 2.82-2.88 (m, 1H) 2.71-2.79 (m, 1H) 2.41-2.50 (m, 1H) 2.19-2.35 (m, 2H) 1.71-1.85 (m, 1H) 1.94 (br. s., 1H) 1.53-1.73 (m, 3 H) 0.90 (s, 9 H) 0.07 (s, 6 H).

DESCRIPCION 74

cis-2-[3,5-bis(trifluorometil)fenil]-N-[6-[1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirrolo[1,2-a]pirazin-2(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D74)



A una solución de *cis*-1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirrolo[1,2-*a*]pirazina (D73, 50 mg) en tolueno seco (0.5 ml), se añadió una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-

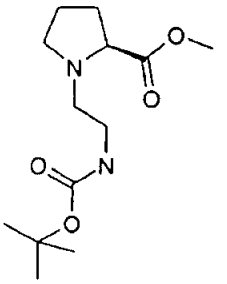
metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (75 mg) en tolueno seco (0.5 ml) a t.a. Se añadieron cloruro de hexadeciltrimetilamonio (solución acuosa al 25%, 132 microlitros), bis(tri-ter-butilfosfino)paladio (19 mg) y NaOH (solución acuosa al 50%, 245 microlitros). La mezcla resultante se desgasificó por dos ciclos de congelamiento-descongelamiento y se dejó que alcanzara t.a. bajo una atmósfera de nitrógeno. La mezcla después se calentó a 90°C durante 5 horas. La mezcla se dejó enfriar a t.a., se diluyó con acetato de etilo (1 ml) y se lavó con una solución saturada de $NaHCO_3$ (1 ml). La fase acuosa se extrajo con acetato de etilo (3 x 2.5 ml). Los extractos orgánicos combinados se secaron y se concentraron bajo vacío a un residuo que se purificó por cromatografía instantánea (Cycl/EtOAc 1:1) para dar el compuesto deseado (10.5 mg) como aceite amarillo.

CCD: Cycl/EtOAc 1:1, Rf=0.49.

UPLC/EM: pico a Tr = 0.87 min con m/z = 767 $[M+H]^+$.

DESCRIPCION 75

1-[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]-L-prolinato de metilo (D75)



A una solución de L-prolinato de metilo (892 mg, 6.93 mmoles)

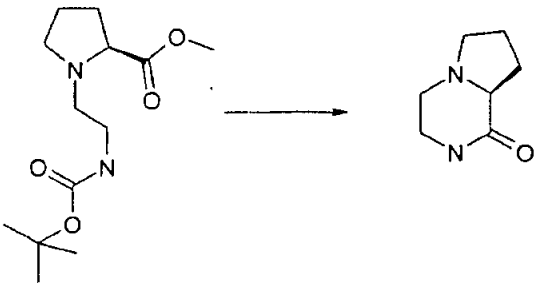
360

en dicloroetano (20 ml) se añadió a t.a. (2-oxoetil)carbamato de 1,1-dimetiletilo (1 g, 6.3 mmoles) y la mezcla de reacción se agitó durante 30 min. Se añadió triacetoxiborhidruro de sodio (2.34 g, 12.6 mmoles) y la mezcla de reacción se agitó durante 3 hr. El compuesto del título (1 g) se aisló después de purificación mediante SCX.

^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 5.11-5.49 (m, 1H) 3.59-3.88 (m, 4 H) 3.05-3.41 (m, 4 H) 2.71-2.90 (m, 1H) 2.54-2.73 (m, 1H) 2.34-2.51 (m, 1H) 2.03-2.30 (m, 1H) 1.27-2.04 (m, 11 H).

DESCRIPCION 76

(8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-1(2*H*)-ona (D76)



A una solución de 1-[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]-L-prolinato de metilo (D75, 1 g) en diclorometano (20 ml) se añadió a t.a. TFA (5 ml) y la mezcla de reacción se agitó durante 1 hr. La mezcla se diluyó con MeOH y se filtró a través de un cartucho de SCX. Las fracciones eluidas con amoniaco metanólico se evaporaron bajo vacío manteniendo la temperatura del baño a 40°C.

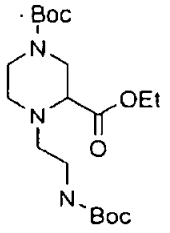
El crudo se purificó por cromatografía (cartucho de sílice,

CH_2Cl_2:MeOH 95:5) para dar el compuesto del título (420 mg).

^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 5.86-6.38 (m, 1H) 3.47-3.70 (m, 1H) 3.24-3.47 (m, 2H) 2.87-3.13 (m, 3 H) 2.65-2.87 (m, 1H) 2.14-2.37 (m, 1H) 1.69-2.10 (m, 3 H)

DESCRIPCION 77

4-[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]-1,3-piperazinadicarboxilato de 1-(1,1-dimetiletil) 3-etilo (D77)

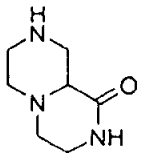


A una solución de 1,3-piperazinadicarboxilato de 1-(1,1-dimetiletil) 3-etilo [EP1486498, 2004] (2.023 g, 8.28 mmoles) en 10 ml de dicloroetano se añadió una solución de *N*-boc-2-aminoacetaldehído (1.87 g, 12.42 mmoles) en 20 ml de dicloroetano. La solución se agitó a temperatura ambiente y bajo atmósfera de nitrógeno durante 30 min. Triacetoxiborhidruro de sodio (3.32 g, 16.56 mmoles) después se añadió y la reacción mantuvo la temperatura ambiente durante la noche. El producto se aisló sobre un cartucho de SCX. 2.492 g.

CL/EM: pico a 2.16 min, m/z= 402 (M+1).

DESCRIPCION 78

Hexahidro-2*H*-pirazino[1,2-a]pirazin-1(6H)-ona (D78)

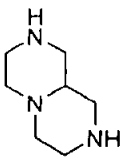


A una solución de 4-[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil]-1,3-piperazinadicarboxilato de 1-(1,1-dimetiletil) 3-etilo (D77, 2.492 g, 6.21 mmoles) en diclorometano (30 ml) mantenida a 0°C se añadió TFA (10 ml) gota a gota. La solución se mantuvo a 0°C durante 2 hr, y después a temperatura ambiente durante 6 hr. El producto desprotegido se aisló por SCX y la solución resultante se evaporó a 50°C para inducir ciclización. El producto objetivo se purificó por cromatografía de fase inversa (columnas Oasis HLB 6g x 4, eluidas con agua), obteniendo 372 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.65 (br. s., 1H) 3.20-3.30 (m, 2H) 2.98-3.07 (m, 1H) 2.84 (d, 1H) 2.72-2.80 (m, 2H) 2.68 (dt, 1H) 2.49-2.52 (m, 1H) 2.40-2.46 (m, 1H) 2.35 (dt, 1H) 2.12 (dt, 1H).

DESCRIPCION 79

Octahidro-2*H*-pirazino[1,2-a]pirazina (D79)



A una suspensión de hexahidro-2*H*-pirazino[1,2-*a*]pirazin-1 (6*H*)-

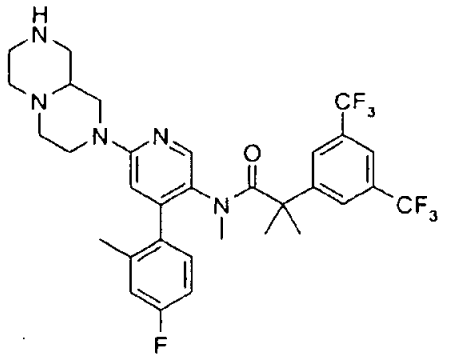
ona (D78, 339 mg, 2.184 mmoles) en 3.5 ml de THF mantenida a 0°C se añadieron gota a gota 21.84 ml de una solución de borano-THF 1 M. La reacción se mantuvo a 75°C bajo atmósfera de nitrógeno durante 3 hr, después se extinguió mediante la adición lenta de MeOH a 0°C. Después de 30 min a temperatura ambiente, se añadieron 5 ml de una solución de HCl acuosa al 37% diluida en 10 ml de MeOH y la solución resultante se calentó a 50°C durante 2.5 hr. El solvente se removió y el residuo se purificó por SCX, dejando 251 mg del compuesto del título.

EM (directo): m/z= 142 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 2.44-2.77 (m, 8 H) 2.17 (t, 2H) 1.97 (dt, 2H) 1.73-1.84 (m, 1H)

DESCRIPCION 80

2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(octahidro-2*H*-pirazino[1,2-a]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida (D80)



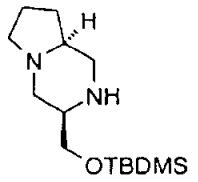
A una solución de octahidro-2*H*-pirazino[1,2-a]pirazina (D79, 197 mg, 1.395 mmoles) en 6 ml de DMSO se añadió 2-[3,5-bis(trifluorometil)fenil]-

N-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-N,2-dimetilpropanamida [WO 2005/002577] (372 mg, 0.698 mmoles) y carbonato de potasio (289 mg, 2.09 mmoles) y la reacción se calentó a 130°C durante 22 hr. El producto se aisló por SCX, y el crudo obtenido (451 mg) se usó en las siguientes reacciones sin purificación adicional.

EM (directo): m/z= 638 (M+1).

DESCRIPCION 81

(3*R*,8a*S*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirrolo[1,2-*a*] pirazina (D81)



A una solución de (3*R*,8a*S*)-octahidropirrolo[1,2-*a*]pirazin-3-ilmetanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005), 220 mg, 1.41 mmoles) en 8 ml de diclorometano se añadió trietilamina (262 µl, 2.82 mmoles) y una solución de cloruro de ter-butildimetlilsililo (170 mg, 1.7 mmoles) en diclorometano (1 ml) y la solución se agitó a temperatura ambiente durante 3 hr. Se añadió cloruro de ter-butildimetlilsililo adicional (113 mg, 1.1 mmoles) y la solución se dejó a temperatura ambiente durante la noche. Más trietilamina (261 µl, 2.82 mmoles) y cloruro de ter-butildimetlilsililo (71 mg, 0.69 mmoles) se añadieron nuevamente, y la reacción se dejó a temperatura ambiente durante 5 hr. La reacción se diluyó con diclorometano y

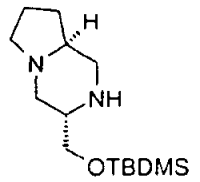
se extrajo con $NaHCO_3$ saturado y salmuera. El producto se aisló por cromatografía instantánea (diclorometano a diclorometano:NH_3 0.5 M en MeOH 9:1), obteniendo 259 mg del compuesto del título.

^{1}H RMN (500 MHz, CLOROFORMO-*d*) δ ppm 3.89 (t, 1H) 3.60 (dd, 1H) 3.01-3.10 (m, 3 H) 2.95 (dt, 1H) 2.79 (dd, 1H) 2.75 (dd, 1H) 2.49 (dd, 1H) 2.23-2.40 (m, 2H) 1.66-1.89 (m, 3 H) 1.43-1.57 (m, 1H) 0.90 (s, 9 H) 0.08 (s, 6 H)

CL/EM (verificación a 5 hr de reacción): pico a 0.49 min, m/z= 271 (M+1).

DESCRIPCION 82

(3*S*,8a*S*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirrolo[1,2-*a*] pirazina (D82)



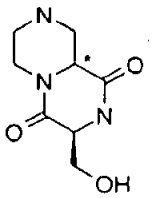
A una solución de (3*RS*,8a*S*)-octahidropirrolo[1,2-a]pirazin-3-ilmetanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005) (531.5 mg, 3.39 mmoles) en 20 ml de diclorometano se añadió trietilamina (1.423 ml, 10.17 mmoles) y cloruro de ter-butildimetlilsililo (1.026 g, 6.78 mmoles). La solución se agitó a temperatura ambiente durante 2 días. La reacción se diluyó con diclorometano y se extrajo con $NaHCO_3$ saturado y salmuera. El producto se aisló por cromatografía instantánea (diclorometano a diclorometano:MeOH

99:1 a 90:10), obteniendo 157 mg del compuesto del título.

^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 3.60-3.70 (m, 1H) 3.47-3.59 (m, 1H) 2.90-3.28 (m, 3 H) 2.50-2.73 (m, 1H) 2.09-2.30 (m, 1H) 1.79-2.09 (m, 2H) 1.37-1.80 (m, 5 H) 0.87-0.97 (s, 9 H) 0.03-0.13 (s, 6 H).

DESCRIPCION 83 y 84

(3*S*, 9a*S* o 9a*R*)-3-(hidroximetil)tetrahidro-2*H*-pirazino[1,2-a]pirazina-1,4(3*H*,6*H*)-diona (D83-Diaestereoisómero 1) y (3*S*, 9a*R* o 9a*S*)-3-(hidroximetil)tetrahidro-2*H*-pirazino[1,2-*a*]pirazina-1,4(3*H*,6*H*)-diona (D84-Diaestereoisómero 2)



A una solución del ácido *N,N'*-di-boc-piperazin-2-carboxílico (2 g) en 60 ml de diclorometano se añadió HOBt (817 mg) y EDC (1.74 g). La reacción se agitó durante 30 min. Mientras tanto, se preparó una solución de clorhidrato de éster L-serinmetílico (1.413 g, n mmoles) y diisopropiletilamina (1.62 ml) en 20 ml de diclorometano y finalmente se añadió a la mezcla de reacción. La reacción se dejó agitar a temperatura ambiente durante la noche. El análisis de UPLC-EM mostró el producto esperado (pico a 0.67 min, m/z = 432 (M+1), 376 (M-*t*-Bu), 320 (M-Boc +1)). La reacción se diluyó con diclorometano y se extrajo con $NaHCO_3$ saturado, se secó (Na_2SO_4), y el

solvente se removió. El crudo (2.75 g) se recogió para el siguiente paso sin purificación adicional.

Se disolvió en 30 ml de diclorometano y se trató con 10 ml de TFA, añadidos a 0°C. La reacción se agitó a temperatura ambiente durante 1.5 hr. Se verificó por UPLC/MS, que mostró el producto de desprotección esperado a 0.20 min, m/z = 232 (M+1). El crudo se purificó por SCX. Las fracciones básicas se agitaron a 50°C y se evaporaron. El sólido así obtenido se suspendió en 5 ml de MeOH y se filtró para dar el compuesto del título (D83-diaestereoisómero 1) como un sólido blanco 333 mg.

D 83:

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.99 (s, 1H) 5.07 (t, 1H) 4.15 (dd, 1H) 3.67-3.77 (m, 3 H) 3.40-3.49 (m, 1H) 3.20 (dd, 1H) 2.82 (dd, 1H) 2.45-2.52 (m, 1H) 2.31- 2.42 (m, 2H)

UPLC/MS: Pico a 0.16 min, m/z= 200 (M+1).

La solución se concentró para dar un segundo sólido (976 mg) como una mezcla de los compuesto del título: (mezcla de D83-diaestereoisómero 1 y D84-diaestereoisómero 2).

D83+D84:

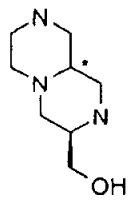
^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.93-8.08 (m, 1H) 5.06-5.19 (m, 1H) 4.14-4.33 (m, 1H) 3.67-3.77 (m, 3 H) 3.40-3.49 (m, 1H) 3.11-3.23 (m, 1H) 2.75-2.90 (m, 1H) 2.45-2.52 (m, 1H) 2.31-2.42 (m, 2H).

UPLC/MS: Pico a 0.16 min, m/z= 200 (M+1).

DESCRIPCION 85

(3*R*,9a*S* o 9a*R*)-octahidro-2*H*-pirazino[1,2-a]pirazin-3-ilmetanol

(D85-Diaestereoisómero 1)

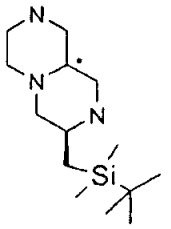


A un matraz que contenía (3*S*, 9a*S* o 9a*R*)-3-(hidroximetil)tetrahidro-2*H*-pirazino[1,2-a]pirazina-1,4(3*H*,6*H*)-diona (D83, 217 mg) se añadió solución de BH_3-THF 1M (10.9 ml) y la reacción se llevó a reflujo (80°C) durante la noche. El matraz de reacción se enfrió a 0°C y se trató con 20 ml de MeOH y HCl concentrado (2.5 ml). La solución resultante se calentó a 60°C durante 4 hr. La reacción se verificó por EM directa (m/z= 172 (M+1), 184 ($M+BH_3$)). La mezcla de reacción se purificó por SCX, obteniendo 174 mg del compuesto del título.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 4.39-4.63 (m, 1H) 3.17-3.26 (m, 2H) 2.56-2.79 (m, 6 H) 2.14-2.31 (m, 2H) 1.92-2.04 (m, 1H) 1.72-1.85 (m, 1H) 1.66 (t, 1H).

DESCRIPCION 86

(3*R*,9a*S* o 9a*R*)-3-{[(1,1-dimetiletil)(dimetil)silil]metil}octahidro-2*H*-pirazino[1,2-*a*]pirazina (D86 - Diaestereoisómero 1)



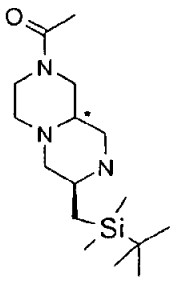
El (3*R*, 9a*S* o 9a*R*)-octahidro-2*H*-pirazino[1,2-*a*]pirazin-3-ilmetanol de partida (D85, 173 mg) se disolvió en 6 ml de diclorometano y se trató con Et_3N (420 µl) y TDBMSCl (305 mg). La reacción se agitó a temperatura ambiente durante 3 días. Más TDBMSCl (144 mg, n mmoles) se añadió y la reacción se agitó nuevamente durante la noche. Se verificó por UPLC/MS, que mostró conversión al producto: pico a 0.47 min, m/z = 286 (M+1). El crudo se purificó por cromatografía instantánea (sílice, CH_2Cl_2 a CH_2Cl_2: (NH_3 0.5 M en MeOH) 90:10), para dar 218 mg del producto esperado.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.34-3.53 (m, 2H) 2.92-3.12 (m, 2H) 2.60-2.92 (m, 6 H) 2.26-2.39 (m, 1H) 2.11-2.27 (m, 1H) 1.98-2.11 (m, 1H) 1.70-1.83 (m, 1H) 1.23 (t, 1H) 0.80-0.92 (m, 9 H) -0.02-0.09 (m, 6 H).

370

DESCRIPCION 87

(7*R*, 9a*R* o 9a*S*)-2-acetil-7-{[(1,1-dimetiletil)(dimetil)silil]metil}octahidro-2*H*-pirazino[1,2-*a*]pirazina (D87-Diaestereoisómero 1)



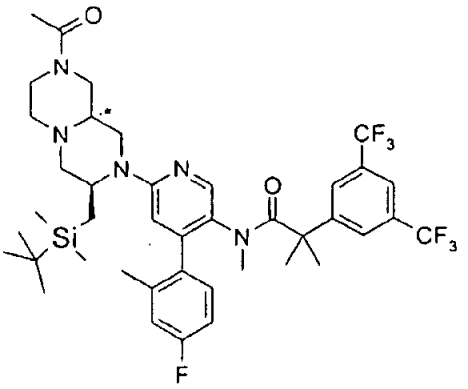
A una solución de la (3*R*, 9a*S* o 9a*R*)-3-{[(1,1-dimetiletil)(dimetil) silil]metil}octahidro-2*H*-pirazino[1,2-*a*]pirazina (D86, 217 mg) en 9 ml de diclorometano se añadió trietilamina (212 µl) y se llevó a –10°C. Se añadió gota a gota una solución de cloruro de acetilo (54 µl) en 2 ml de diclorometano. Después de 15 min, la reacción se extinguió mediante la adición de MeOH. El crudo se purificó por cromatografía instantánea (sílice, CH_2Cl_2 a CH_2Cl_2: (NH_3 0.5 M en MeOH) 95:5). La muestra así obtenida se disolvió en CH_2Cl_2 y se extrajo con $NaHCO_3$ saturado. Los compuestos orgánicos se secaron y el solvente se removió, conduciendo el compuesto del título (128 mg).

CL/EM: m/z=328 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 4.25 (dd, 1H) 3.62 (dd, 1H) 3.36-3.46 (m, 2H) 2.83 (dd, 1H) 2.62-2.76 (m, 4 H) 2.55-2.62 (m, 1H) 2.26-2.33 (m, 1H) 1.96 (s, 3 H) 1.85-1.92 (m, 1H) 1.80 (t, 1H) 1.67 (t, 1H) 0.84 (s, 9 H) 0.01 (s, 6 H).

DESCRIPCION 88

_N_-[6-((3_R_, 9a_R_ o 9a_S_)-8-acetil-3-{[(1,1-dimetiletil)(dimetil)silil] metil}octahidro-2_H_-pirazino[1,2-_a_]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-_N_,2-dimetilpropanamida (D88-Diaestereoisómero 1)

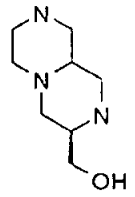


A una solución de (7_R_, 9a_R_ o 9a_S_)-2-acetil-7-{[(1,1-dimetiletil) (dimetil)silil]metil}octahidro-2_H_-pirazino[1,2-_a_]pirazina (D87, 125 mg, 5.72 mmoles) en 1.5 ml de tolueno se añadió 2-[3,5-bis(trifluorometil)fenil]-_N_-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-_N_,2-dimetilpropanamida [WO 2005/002577] (156 mg, n mmoles), bis-tri-ter butilfosfinpaladio (30 mg, n mmoles), cloruro de hexadeciltrimetilamonio (19 µl de una solución acuosa al 25%) y, por último, solución de hidróxido de sodio (35 µl de una solución acuosa al 50%). La solución se desgasificó por ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C durante 3.75 hr. Se verificó por UPLC/MS, que mostró picos para el producto esperado a 0.94 min. (m/z = 824 (M+1), 412 (M+2)/2). La solución se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado y salmuera. El producto se aisló por cromatografía

instantánea (ciclohexano:EtOAc 50:50 → 0:100), obteniendo 149 mg del compuesto del título que se llevó directamente para el siguiente paso.

DESCRIPCION 89

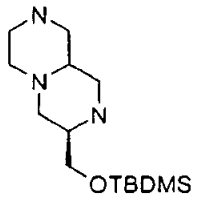
(3*R*)-octahidro-2*H*-pirazino[1,2-*a*]pirazin-3-ilmetanol (D89)



A un matraz que contenía (3*S*, 9a*S* o 9a*R*)-3-(hidroximetil)tetrahidro-2*H*-pirazino[1,2-*a*]pirazina-1,4(3*H*,6*H*)-diona y (3*S*, 9a*R* o 9a*S*)-3-(hidroximetil)tetrahidro-2*H*-pirazin[1,2-*a*]pirazina-1,4(3*H*,6*H*)-diona (D83, diaestereoisómero 1 más D84, diaestereoisómero 2, 976 mg, 4.9 mmoles) se añadió solución de BH_3-THF 1M (49 ml) bajo nitrógeno y la reacción se llevó a reflujo (80°C) durante la noche. El matraz de reacción se enfrió a 0°C y se trató con 25 ml de MeOH. Se añadió HCl concentrado y la solución resultante se calentó a 60°C durante 5 hr. La reacción se verificó por EM directa (m/z= 184 ($M+BH_3$)). La mezcla de reacción se purificó por SCX, obteniendo 528 mg de producto.

DESCRIPCION 90

(3*R*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-2*H*-pirazin[1,2-*a*] pirazina (D90)

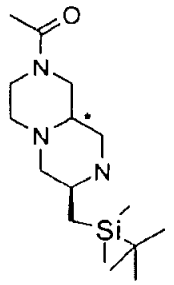


El (3*R*)-octahidro-2*H*-pirazino[1,2-*a*]pirazin-3-ilmetanol (D89, 528 mg, 3.08 mmoles) de partida se disolvió en 20 ml de diclorometano y se trató con Et_3N (1.29 ml, 9.25 mmoles) y TDBMSCl (929.5 mg, 6.17 mmoles). La reacción se agitó a temperatura ambiente durante la noche y después durante 24 hr adicionales. Se verificó por UPLC/MS, que mostró conversión a producto: pico a 0.47 min, m/z = 286 (M+1), 172 (M-TBDMS+1). El crudo se purificó por cromatografía instantánea (sílice, CH_2Cl_2 : (NH_3 0.5 M en MeOH) 98:2 a 85:15). El residuo se obtuvo evaporando las fracciones que contenía el producto, se disolvió en diclorometano:MeOH 90:10 y el material insoluble se filtró. La solución se evaporó para dar 638 mg del producto objetivo.

^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 4.02-4.15 (m, 1H) 3.82-3.95 (m, 1H) 3.52-3.67 (m, 2H) 3.30-3.49 (m, 3 H) 3.03-3.19 (m, 1H) 2.91-3.03 (m, 1H) 2.66-2.89 (m, 6 H) 1.50 (t, 1H) 0.85-0.96 (m, 9 H) 0.05-0.16 (m, 6 H).

DESCRIPCION 91

(7*R*,9a*S* o 9a*R*)-2-acetil-7-{[(1,1-dimetiletil)(dimetil)silil]metil}octahidro-2*H*-pirazino[1,2-*a*]pirazina (D91- Diaestereoisómero 2)



A una solución de (3*R*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidro-2*H*-pirazino[1,2-*a*]pirazina (D90, 635 mg, 2.224 mmoles) en 15 ml de diclorometano se añadió trietilamina (620 µl, 4.45 mmoles) y se llevó a –10°C. Se añadió gota a gota una solución de cloruro de acetilo (79 µl, 1.11 mmoles, 0.5 eq.) en 0.5 ml de diclorometano. La reacción se llevó a -45°C y se añadieron 0.25 eq. adicionales (39.5 µl) de cloruro de acetilo diluidos en 0.5 ml de diclorometano. La temperatura se redujo a –50°^{0}C y se añadieron nuevamente 0.25 eq. (39.5 µl) de cloruro de acetilo diluidos en 0.5 ml de diclorometano. El crudo se purificó por cromatografía instantánea (sílice, CH_2Cl_2 a CH_2Cl_2 : (NH_3 0.5 M en MeOH) 95:5). Se obtuvo así una muestra del compuesto del título limpio: 121 mg.

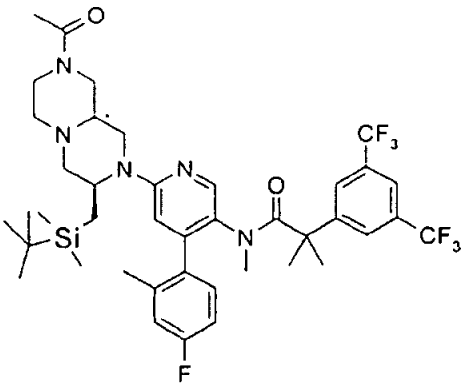
EM (directo): m/z=328 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 4.25 (d, 1H) 3.77 (t, 1H) 3.67-3.74 (m, 2H) 3.11 (t, 1H) 2.63-2.78 (m, 2H) 2.53-2.61 (m, 2H) 2.34-2.46 (m, 2H) 2.11 (dd, 1H) 1.95-2.03 (m, 1H) 1.96 (s, 3 H) 1.82-1.90 (m, 1H) 0.83-

0.90 (m, 9 H) 0.04 (s, 6 H).

DESCRIPCION 92

_N_-[6-((3_R_, 9a_S_ o 9a_R_)-8-acetil-3-{[(1-dimetiletil)(dimetil)silil] metil}octahidro-2_H_-pirazino[1,2-_a_]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-_N_,2-dimetilpropanamida (D92-Diaestereoisómero 2)

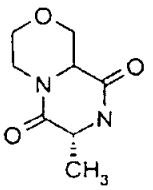


A una solución de (7_R_, 9a_S_ o 9a_R_)-2-acetil-7-{[(1,1-dimetiletil) (dimetil)silil]metil}octahidro-2_H_-pirazino[1,2-_a_]pirazina (D91, 117 mg, 0.357 mmoles) en 1.5 ml de tolueno se añadió 2-[3,5-bis(trifluorometil)fenil]-_N_-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-_N_,2-dimetilpropanamida [WO 2005/002577] (146.5 mg, 0.275 mmoles), bis-tri-ter-butilfosfinopaladio (28 mg, 0.055 mmoles), cloruro de hexadeciltrimetilamonio (18 µl de una solución acuosa al 25%) y, por último, solución de hidróxido de sodio (33 µl de una solución acuosa al 50%). La solución se desgasificó por ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C durante 3 hr. Se verificó por UPLC/MS, que mostró picos para el producto esperado a

1.21 min. (m/z = 824 (M+1), 412 (M+2)/2). La solución se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado y salmuera. El compuesto del título se aisló por cromatografía instantánea (sílice, ciclohexano: EtOAc 50:50 → 0:100), obteniendo 199 mg que se llevó directamente para el siguiente paso.

DESCRIPCION 93

(3*R*)-3-metiltetrahidro-2*H*-pirazino[1,2-*a*]pirazina-1,4(3*H*,6*H*)-diona (D93)



A una solución de ácido *N*-boc-morfolin-3-carboxílico (2 g, 9.379 mmoles) en 60 ml de diclorometano se añadió TBTU (3.313 g, 10.32 mmoles) y diisopropiletilamina (1.96 ml, 11.25 mmoles). La reacción se agitó durante 30 min. Mientras tanto, una solución de clorhidrato de éster D-alaninmetílico (1.93 g, 18.76 mmoles) y diisopropiletilamina (3.27 ml, 18.76 mmoles) en 20 ml de diclorometano se preparó y finalmente se añadió a la mezcla de reacción. La reacción se dejó agitar a temperatura ambiente durante 2 hr. El análisis de UPLC-EM mostró el producto esperado (pico a 0.60 min, m/z = 317 (M+1), 261 (M-*t*-Bu+1), 217 (M-Boc +1)). La reacción se diluyó con diclorometano y se extrajo con $NaHCO_3$ saturado, se secó (Na_2SO_4), y el solvente se removió. El crudo (5.56 g) se recogió para el siguiente paso sin purificación adicional.

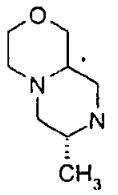
Este se disolvió en 50 ml de diclorometano y se trató con 50 ml de TFA, añadidos a 0°C. La reacción se agitó a temperatura ambiente durante

30 min. Se verificó por UPLC/MS, que mostró el producto de desprotección esperado. El crudo se purificó por SCX. Las fracciones que contenía el producto se concentraron y la solución resultante se agitó a 50°C durante 9 hr y a 80°C durante 19 hr adicionales. El análisis de UPLC/MS mostró formación del producto ciclizado: pico a 0.34 min, m/z= 185 (M+1). La solución se corrió a través de un cartucho de SCX y así se obtuvo el compuesto del título, 1.095 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.36 (br. s., 1H) 3.80-4.22 (m, 5 H) 3.33-3.41 (m, 2H) 2.68-2.84 (m, 1H) 1.25-1.37 (m, 3 H).

DESCRIPCION 94 y 95

(7*R*, 9a*R* o 9a*S*)-7-metiloctahidropirazino[2,1-*c*][1,4]oxazina (D94 - Diaestereoisómero 1) y (7*R*, 9a*S* o 9a*R*)-7-metiloctahidropirazino[2,1-*c*][1,4]oxazina (D95 - Diaestereoisómero 2)



A un matraz que contenía (3*R*)-3-metiltetrahidro-2*H*-pirazino[1,2-*a*]pirazina-1,4(3H,6*H*)-diona, mezcla de diaestereómeros, (D93, 923 mg, 5.01 mmoles) se añadió solución de BH_3-THF 1M (50 ml) y se calentó a 90°C durante 14 hr. A la suspensión se añadieron 30 ml de HCl 6M y se calentó a 90°C durante 2 hr. Análisis de EM: m/z= 157 (M+1 del producto objetivo). La

mezcla de reacción se purificó por SCX, seguido por cromatografía instantánea (sílice, diclorometano: (NH_3 en MeOH) = 95:5 a 80:20. Se aislaron los dos compuestos del título.

Diaestereoisómero 1 (D94) (102 mg):

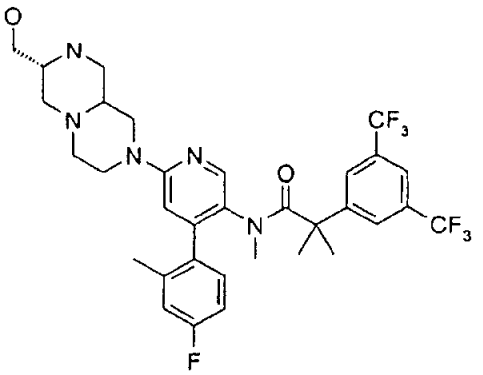
^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.65-3.73 (m, 1H) 3.53-3.60 (m, 1H) 3.43-3.52 (m, 1H) 3.02 (t, 1H) 2.68-2.81 (m, 1H) 2.52-2.68 (m, 3 H) 2.25 (t, 1H) 2.07-2.19 (m, 1H) 1.88-2.00 (m, 1H) 1.68 (t, 1H) 0.91 (d, 3 H)

Diaestereoisómero 2 (D95) (29 mg):

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.63-3.72 (m, 1H) 3.46-3.56 (m, 2H) 3.09 (t, 1H) 2.95-3.03 (m, 1H) 2.31-2.47 (m, 3 H) 2.17-2.24 (m, 1H) 2.06-2.17 (m, 1H) 1.87-2.04 (m, 1H) 1.21-1.28 (m, 1H) 1.17 (d, 3H)

DESCRIPCION 96

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*R*)-7-(hidroximetil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (D96)



A una solución de (3*R*)-octahidro-2*H*-pirazino[1,2-*a*]pirazin-3-

380

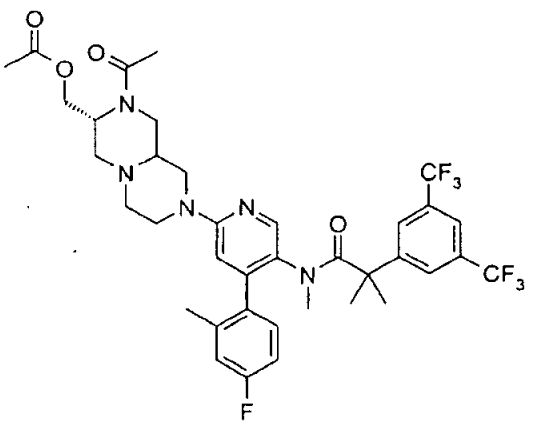
ilmetanol (D89, mezcla de diaestereoisómeros de relación no conocida, 83.5 mg, 0.496 mmoles) en 1.6 ml de DMSO se añadieron K_2CO_3 (78 mg) y 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (100 mg). La reacción se dejó a 150°C durante 23 hr. Se verificó por UPLC/MS, que mostró un pico para el producto esperado a 0.71 min. (m/z = 668 (M+1), 334 (M+2)/2). La solución se diluyó con diclorometano, se extrajo con agua y se secó (Na_2SO_4). El compuesto del título obtenido (113.5 mg) se recogió para el siguiente paso sin purificación adicional.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.02 (br. s., 1H) 7.88 (br. s., 1H) 7.71 (br. s., 2H) 7.01-7.25 (m, 3 H) 6.62-6.75 (m, 1H) 4.38-4.58 (m, 1H) 4.14-4.30 (m, 1H) 4.00-4.15 (m, 1H) 3.58-3.70 (m, 1H) 3.49-3.59 (m, 1H) 3.20-3.36 (m, 2H) 2.79-2.93 (m, 2H) 2.63-2.79 (m, 4 H) 2.02-2.35 (m, 6 H) 1.83-2.02 (m, 1H) 1.13-1.58 (m, 6 H)

No se determinó la relación de diaestereoisómeros.

DESCRIPCION 97

Acetato de {(3*R*)-2-acetil-8-[5-[{2-[3,5-bis(trifluorometil)fenil]-2-metilpropanoil}(metil) amino]-4-(4-fluoro-2-metilfenil)-2-piridinil]octahidro-2*H*-pirazino[1,2-*a*] pirazin-3-il}metilo (D97)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*R*)-7-(hidroximetil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (D96, 56 mg, 0.0838 mmoles) en 10 ml de diclorometano se añadieron Et_3N (35 µl) y una solución de cloruro de acetilo (15 µl) en diclorometano (0.3 ml). La reacción se agitó a temperatura ambiente durante 3 hr. Se verificó por UPLC/MS, que mostró un pico para el producto esperado a 0.89 min. (m/z = 752 (M+1), 376 (M+2)/2). La solución se diluyó con diclorometano, se extrajo con agua y se secó (Na_2SO_4). El crudo se purificó por cromatografía instantánea (ciclohexano a EtOAc), obteniendo 28.5 mg del compuesto del título.

^{1}H RMN (400 MHz, CLOROFORMO-*d*) δ ppm 8.00 (br. s., 1H) 7.78 (br. s., 1H) 7.65 (br. s., 2H) 6.80-7.08 (m, 3 H) 6.41- 6.52 (m, 1H) 4.42-

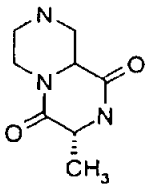
4.70 (m, 2H) 4.17-4.40 (m, 2H) 3.95-4.17 (m, 2H) 3.53-3.65 (m, 1H) 2.98-3.26 (m, 2H) 2.74-2.93 (m, 3 H) 2.49-2.74 (m, 3 H) 2.21- 2.47 (m, 5 H) 2.02-2.21 (m, 9 H) 1.46-1.55 (m, 3 H).

UPLC/MS: pico a 0.89 min. m/z = 752 (M+1), 376 (M+2)/2.

No se determinó la relación de diaestereoisómeros.

DESCRIPCION 98

(3*R*)-3-metiltetrahidro-2*H*-pirazino[1,2-*a*]pirazina-1,4(3*H*,6*H*)-diona (D98)



A una solución de ácido *N,N'*-diboc-piperazin-2-carboxílico (2 g, 6.06 mmoles) en 50 ml de diclorometano se añadió TBTU (2.138 g, 6.66 mmoles) y diisopropiletilamina (1.3 ml, 7.26 mmoles). La reacción se agitó durante 45 min. Mientras tanto, una suspensión de clorhidrato de éster D-alaninmetílico (1.249 g, 12.11 mmoles) y diisopropiletilamina (3.27 ml, 18.76 mmoles) en 20 ml de diclorometano y 5 ml de DMF se agitó y finalmente se añadió a la mezcla de reacción. La reacción se dejó agitar a temperatura ambiente durante la noche. El análisis de UPLC-EM mostró el producto esperado (pico a 0.72 min, m/z = 416 (M+1), 360 (M-*t*-Bu+1). La reacción se diluyó con diclorometano y se extrajo con $NaHCO_3$ saturado, se secó (Na_2SO_4), y el solvente se removió. El crudo (4.242 g) se recogió para el

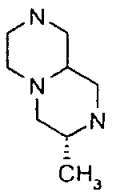
siguiente paso sin purificación adicional.

Este se disolvió en 50 ml de diclorometano y a la solución se añadió gota a gota TFA (50 ml) a 0°C. La reacción se agitó a temperatura ambiente durante 2 hr. Esta se verificó por UPLC/MS. La mezcla de reacción se evaporó y el crudo se purificó por SCX. Las fracciones que contenía el producto se recogieron y su volumen se redujo y la solución resultante se agitó a 60°C durante la noche. El análisis de UPLC/MS mostró formación del producto ciclizado: pico a 0.17 min, m/z= 184 (M+1). El solvente se removió y el residuo recogido se trató en metanol. El precipitado blanco se recogió por filtración, dando 353 mg del compuesto del título (156 mg adicionales del precipitado formado a partir de la solución).

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.24 (br. s., 0.5 H) 7.96 (br. s., 0.5H) 3.79-4.29 (m, 2H) 3.10-3.31 (m, 1H) 2.73-3.11 (m, 2H) 2.52-2.73 (m, 2H) 1.30 (d, 1.5 H) 1.21 (d, 1.5 H)

DESCRIPCION 99

(3*R*)-3-metiloctahidro-2*H*-pirazino[1,2-a]pirazina (D99)



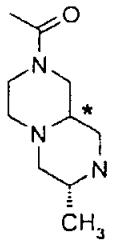
A un matraz que contenía (3*R*)-3-metiltetrahidro-2*H*-pirazino[1,2-*a*]pirazina-1,4(3*H*,6*H*)-diona (D98, 353 mg, 1.927 mmoles) se añadió solución

de BH_3-THF 1M (20 ml) y se calentó a reflujo durante 20 hr. Análisis de EM: m/z= 156 (M+1 del producto objetivo). A la reacción se añadieron, a 0°C, 10 ml de HCl 6M y se calentó a 90°C durante 20 hr. La mezcla de reacción se purificó por SCX, obteniendo 243 mg del compuesto objetivo.

^{1}H RMN (400 MHz, DMSO-d_6) consistente con una mezcla de diaestereómeros del compuesto objetivo.

DESCRIPCION 100 y 101

(7*R*, 9a*R* o 9a*S*)-2-acetil-7-metiloctahidro-2*H*-pirazino[1,2-*a*]pirazina (D100, Diaestereoisómero 1) y (7*R*, 9a*S* o 9a*R*)-2-acetil-7-metiloctahidro-2*H*-pirazino[1,2-*a*]pirazina (D101, Diaestereoisómero 2)



A una solución de (3*R*)-3-metiloctahidro-2*H*-pirazino[1,2-*a*]pirazina (D99, 243 mg, 1.232 mmoles) en DMF (35 ml) se añadió trietilamina (260 µl, 1.848 mmoles). La solución se enfrió a -60°C y una solución de anhídrido acético (95 µl, 0.986 mmoles) en DMF (3 ml) se añadió gota a gota. Se dejó que la reacción alcanzara -60°C lentamente. Análisis de UPLC/MS: picos @ 0.18 y 0.24 min, ambos m/z= 198 (M+1 del producto objetivo). La mezcla de reacción se purificó por SCX, seguido por cromatografía instantánea (sílice, diclorometano a diclorometano:MeOH 85:15) De esta

manera se obtuvieron dos diferentes muestras:

Diaestereoisómero 1 (D100) (101.5 mg):

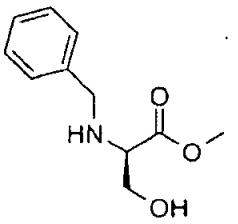
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 4.26 (dd, 1H) 4.16 (dd, 1H) 2.52-2.82 (m, 5 H) 2.26-2.33 (m, 1H) 2.16 (t, 1H) 1.96 (s, 3 H) 1.83-1.90 (m, 1H) 1.56-1.70 (m, 2H) 0.90 (d, 3 H)

Diaestereoisómero 1 y 2 (D100 más D101) (75 mg):

La muestra de RMN consistió una mezcla de dos componentes, relación de aprox. 3:1. El componente mayor es igual al diaestereoisómero 1. El menor parece consistente con su diaestereoisómero 2.

DESCRIPCION 102

N-(fenilmetil)-D-serinato de metilo (D102)



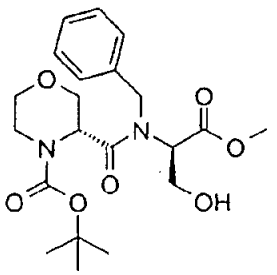
El compuesto del título se preparó de confomridad con la literatura (ref. *JOC*, 1990, *55*(1), 111-122) empezando a partir de clorhidrato de éster (D)-serinmetílico (98%, de Aldrich). Clorhidrato de éster (D)-serinmetílico (10 g, 0.065 moles) se suspendió en 50 ml de metanol anhidro y se enfrió a 0°C bajo nitrógeno. Trietilamina (9 ml, 0.065 moles) se añadió gota a gota, seguido por benzaldehído (6.6 ml, 0.065 moles). La mezcla de reacción después se calentó y se agitó a temperatura ambiente durante 2

horas. Borhidruro de sodio (4.85 g, 0.13 moles) se añadió en porciones pequeñas durante 2 horas. La mezcla resultante se agitó a temperatura ambiente durante la noche. Después, la mezcla lentamente se añadió a 50 ml de HCl (solución al 20%) a 0°C y la solución resultante se lavó con éter dietílico (50 ml). La capa acuosa se llevó después a pH básico añadiendo carbonato de potasio sólido y se extrajo con éter dietílico (3 x 50 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo vacío para dar el compuesto del título como aceite incoloro (10.95 g).

m/z = 210 $[M+H]^+$

DESCRIPCION 103

(3*R*)-3-{[[(1*R*)-1-(hidroximetil)-2-(metiloxi)-2-oxoetil](fenilmetil) amino]carbonil}-4-morfolincarboxilato de 1,1-dimetiletilo (nombre no preferido) (D103)



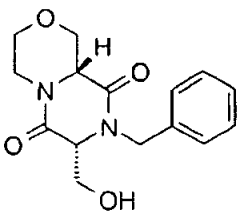
A una suspensión agitada de ácido (R)-4-Boc-morfolin-3-carboxílico (30 g, 0.13 moles, de J&W PharmLab) en 500 ml de DCM anhidro a temperatura ambiente bajo nitrógeno, se añadieron en porciones clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (37.4 g, 0.195 moles) y 1-

hidroxibenzotriazol hidratado (19.3 g, 0.143 moles). Al final de la adición, la suspensión casi se hizo una solución clara. La mezcla se agitó a temperatura ambiente durante 45 minutos y después *N*-(fenilmetil)-D-serinato de metilo (D102, 28.6g, 0.137 moles) y N,N- diisopropiletilamina (45.3 ml, 0.26 moles) se añadieron en porciones pequeñas. La mezcla se agitó a temperatura ambiente durante 26 horas y después se adicionó con cloruro de amonio (solución sat., 250 ml) y DCM (150 ml). Las fases se separaron y la capa acuosa se extrajo con DCM (3 x 150 ml) y EtAc (1 x 200 ml). Los extractos orgánicos combinados se lavaron con salmuera (2 x 500 ml), se secaron (Na_2SO_4), se concentraron bajo vacío y el residuo se purificó por cromatografía de gel de sílice eluyendo con 0 a 30% de EtOAc/Ciclohexano para dar el compuesto del título como aceite amarillo (38.7 g).

UPLC/MS: pico a Tr = 0.62 min con m/z = 423.1 $[M+H]^+$

DESCRIPCION 104

(7*R*,9a*R*)-7-(hidroximetil)-8-(fenilmetil)hexahidropirazino[2,1-*c*][1,4]oxazina-6,9-diona) (D104)



A una solución agitada de (3*R*)-3-{[[(1*R*)-1-(hidroximetil)-2-(metiloxi)-2-oxoetil](fenilmetil)amino]carbonil}-4-morfolincarboxilato de 1,1-

dimetiletilo (D103, 38.7 g, 0.092 moles) en 400 ml de DCM a temperatura ambiente, se añadió lentamente ácido trifluoroacético (68.3 ml, 0.92 moles). La solución anaranjada resultante se agitó a temperatura ambiente durante la noche. Después se enfrió en un baño de hielo-agua y se llevó a pH = 7-8 añadiendo bicarbonato de sodio (solución sat., 250 ml y como sólido). Las fases se separaron y la capa acuosa se extrajo con DCM (3 x 300 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4), se concentraron bajo vacío para dar un residuo, que se disolvió en 270 ml de metanol y se calentó a 56-58°C durante 2 horas. La mezcla después se dejó enfriar a temperatura ambiente y el solvente se removió bajo vacío para dar un residuo sólido, que se trató con 100 ml de una mezcla de ciclohexano/EtOAc 8/2. La suspensión resultante se agitó a temperatura ambiente durante 30-40 minutos y después el sólido se filtró y se recogió para dar el compuesto del título (18.7 g) como sólido blanco.

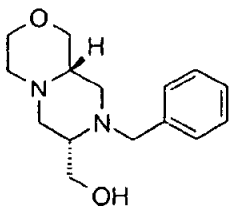
UPLC/MS: pico a Tr = 0.49 min con m/z = 291.09 $[M+H]^+$

^1H RMN (400 MHz, DMSO-d_6) δ ppm 7.26-7.37 (m, 5 H) 5.41 (t, 1H) 5.09 (d, 1H) 4.31 (dd, 1H) 4.23 (dd, 1H) 4.01- 4.07 (m, 2H) 3.69-3.84 (m, 4 H) 3.59 (t, 1H) 3.33 (td, 1H) 2.85 (td, 1H).

DESCRIPCION 105

[(7*S*,9a*S*)-8-(fenilmetil)octahidropirazino[2,1-*c*][1,4]oxazin-7-il]metanol

(D105)



A una suspensión agitada de (7*R*,9a*R*)-7-(hidroximetil)-8-(fenilmetil)hexahidropirazino[2,1-*c*][1,4]oxazina-6,9-diona) (D104, 18.7 g, 0.064 moles) en 190 ml de THF anhidro a 0°C bajo nitrógeno, se añadió borano (solución de complejo de THF, 1 M en THF, 385 ml, 0.386 moles) durante 45 minutos manteniendo la temperatura interna por debajo de 10°C. Al final de la adición, la mezcla se volvió una solución incolora. La mezcla se dejó calentar después a temperatura ambiente y después se calentó a 70°C durante 28 horas. La mezcla después se dejó enfriar a temperatura ambiente y después a 0°C mediante un baño de hielo-agua. Después, se añadió lentamente metanol (47 ml, 1.15 moles) y HCl 6M (32 ml, 0.128 moles), monitoreando cuidadosamente la evolución de gas. La mezcla resultante se dejó calentar después a temperatura ambiente y se agitó durante la noche. La mezcla después se calentó a 55°C durante 8 horas y después se enfrió hasta temperatura ambiente. El precipitado blanco se filtró y el filtrado se concentró bajo vacío para dar un residuo, que se disolvió en 50 ml de agua y 100 ml de DCM. El precipitado blanco que previamente se había filtrado, se recogió y se

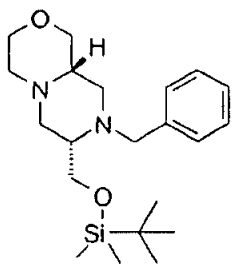
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disolvió en 70 ml de agua y se añadió a la mezcla previa. Las fases se separaron y la capa acuosa se extrajo con DCM (3 x 150 ml). La capa acuosa se llevó después a pH = 7 añadiendo 250 ml de NaOH 3N y se extraj nuevamente con DCM (3 x 100 ml) y acetato de etilo (3 x 200 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo vacío para dar el compuesto del título como espuma amarillo pálido (16.9 g).

UPLC/MS: pico a Tr = 0.40 min con m/z = 263.13 $[M+H]^+$

DESCRIPCION 106

(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-8-(fenilmetil) octahidropirazino[2,1-*c*][1,4]oxazina (D106)



Método a):

A una solución agitada de [(7*S*,9a*S*)-8-(fenilmetil) octahidropirazino[2,1-*c*][1,4]oxazin-7-il]metanol (D105, 15.3 g, 0.058 moles) en 153 ml de DCM a temperatura ambiente, se añadieron imidazol (4.76 g, 0.070 moles) y cloruro de *ter*-butildimetilsililo (8.35 g, 0.055 moles). La mezcla resultante se agitó a temperatura ambiente durante 1 hora. Después, por segunda vez se añadieron imidazol (0.476 g, 5.8 mmoles) y cloruro de ter-

butildimetilsililo (8.35 g, 0.055 moles) y la mezcla se agitó durante la noche. Se añadieron imidazol (0.476 g, 0.006 moles) y cloruro de ter-butildimetilsililo (5.27 g, 0.035 moles) por tercera vez y la mezcla se agitó durante 4 horas adicionales. DCM (153 ml) se añadió y el imidazol (2.4, 0.035 moles) y cloruro de ter-butildimetilsililo (5.27 g, 0.035 moles) se añadieron por cuarta vez. La mezcla se agitó durante la noche. Después, se añadieron agua (150 ml) y bicarbonato de sodio (solución sat., 150 ml) y las fases se separaron. La capa acuosa se extrajo con DCM (150 ml) y los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo vacío a un residuo, se purificaron por cromatografía de gel de sílice eluyendo con 5 a 10% de EtOAc/Ciclohexano para dar el compuesto del título como un aceite (22.2 g).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.32-7.36 (m, 4 H) 7.24-7.29 (m, 1H) 4.00 (t, 1H) 3.90 (dd, 1H) 3.88 (d, 1H) 3.77 (dd, 1H) 3.70 (d, 1H) 3.52-3.58 (m, 1H) 3.48-3.56 (m, 1H) 3.07 (t, 1H) 2.75-2.83 (m, 2H) 2.25-2.37 (m, 4 H) 2.12-2.23 (m, 2H) 0.90 (s, 9 H) 0.08 (s, 3 H) 0.06 (s, 3 H)

CLAR (ascendente): Tr = 4.826 min (% de área = 98.69)

Método b):

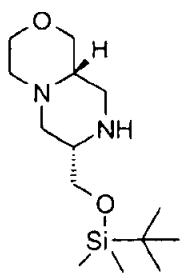
A una solución agitada de [(7*S*,9a*S*)-8-(fenilmetil) octahidropirazino[2,1-*c*][1,4]oxazin-7-il]metanol (D105, 29.8 g, 0.114 moles) en 447 ml de DCM a temperatura ambiente, se añadieron imidazol (9.27 g, 0.136 moles) y cloruro de *ter*-butildimetilsililo (42.7 g, 0.284 moles). La mezcla resultante se agitó a temperatura ambiente durante la noche. Agua (300 ml),

bicarbonato de sodio (solución sat., 300 ml) y DCM (150 ml) después se añadieron y las fases se separaron. La capa acuosa se extrajo con DCM (300 ml) y los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo vacío a un residuo, se purificaron por cromatografía de gel de sílice eluyendo con 5 a 10% de EtOAc/Ciclohexano para dar el compuesto del título como aceite amarillo claro (50.95 g).

CLAR (ascendente): Tr = 4.865 min (% de área = 99.55).

DESCRIPCION 107

(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazin [2,1 *c*] [1,4]oxazina (D107)



A una solución agitada de (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-8-(fenilmetil)octahidropirazino[2,1-*c*][1,4]oxazina (D106, 22.2 g, 0.059 moles) en 660 ml de metanol a temperatura ambiente bajo nitrógeno, se añadieron paladio sobre carbón (10% en peso, húmedo, 6.28 g, 0.006 moles) y formiato de amonio (37.2 g, 0.59 moles). La mezcla resultante se agitó a 80°C durante 1-1.5 horas. La mezcla resultante después se dejó enfriar a temperatura ambiente y se filtró

sobre Celite. El filtrado se concentró bajo vacío para dar el compuesto del título (16 g) como aceite amarillo pálido.

UPLC/MS: pico no visible con UV. Masa m/z = 287.18 $[M+H]^+$

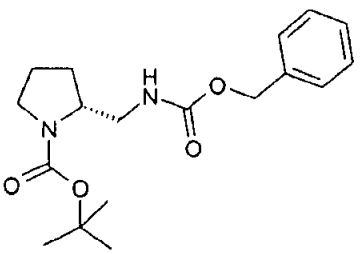
CASS ID 8341, RMN y CL/EM

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 3.74 (t, 1H) 3.62-3.70 (m, 2H) 3.48 (dd, 1H) 3.39-3.46 (m, 1H) 2.98 (t, 1H) 2.67-2.73 (m, 1H) 2.60 (dd, 1H) 2.40 (dd, 1H) 2.26-2.37 (m, 2H) 2.23 (br. s., 1H) 2.12 (dd, 1H) 2.04-2.10 (m, 1H) 1.90-2.00 (m, 1H) 0.81 (s, 9 H) -0.00 (s, 6 H)

Patrón de pico cruzado de ROESY de conformidad con la estereoquímica relativa syn.

DESCRIPCION 108

(2*R*)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidincarboxilato de 1,1-dimetiletilo (D108)



A una solución de (*R*)-2-(aminometil)-1-N-Boc-pirrolidina (1.6 g, 8 mmoles) en 25 ml de diclorometano se añadió DIPEA (2.09 ml, 12 mmoles) y, a 0°C, cloroformiato de bencilo (1.36 ml, 9.6 mmoles). La mezcla de reacción se calentó hasta t.a. y después se agitó durante 3 hr a esta temperatura.

Se añadió salmuera a la mezcla de reacción, la fase acuosa se

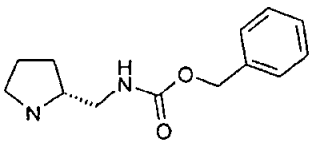
extrajo con diclorometano y las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (cartucho de sílice, ciclohexano: EtOAc 9:1) para dar el compuesto del título (2.07 g, rendimiento = 77%).

EM: m/z= 357 (M+Na) y 235 (M-BOC+1).

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 6.98-7.49 (m, 6 H) 4.88-5.15 (m, 2H) 3.58-3.83 (m, 1H) 3.05-3.32 (m, 3 H) 2.75-3.04 (m, 1H) 1.52-1.98 (m, 4 H) 1.20-1.49 (m, 9 H)

DESCRIPCION 109

[(2*R*)-2-pirrolidinilmetil]carbamato de fenilmetilo (D109)

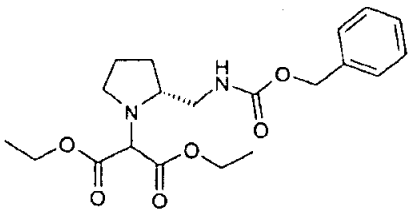


A una solución de (2*R*)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidincarboxilato de 1,1-dimetiletilo (D108, 2.07 g, 6.1 mmoles) en 16 ml de diclorometano, enfriada a 0°C, se añadieron 4 ml de TFA. La mezcla de reacción se dejó calentar hasta t.a. y después se agitó a esta temperatura durante 30 min. El compuesto del título (1.06 g, rend = 88%) se aisló después de purificación por SCX.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.00-7.66 (m, 5 H) 4.90-5.20 (m, 2H) 3.12-3.24 (m, 1H) 2.97-3.09 (m, 1H) 2.84-2.97 (m, 2H) 2.61-2.82 (m, 2H) 1.44-1.83 (m, 3 H) 1.14-1.40 (m, 1H)

DESCRIPCION 110

{(2*R*)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidinil} propanodioato de dietilo (D110)



A una mezcla de [(2*R*)-2-pirrolidinilmetil]carbamato de fenilmetilo (D109, 1.26 g, 5.38 mmoles) y K_2CO_3 (1.48 g, 10.76 mmoles) en acetonitrilo (20 ml), enfriada a 0°C, se añadió gota a gota bromomalonato de dietilo (1.08 ml, 6.46 mmoles) en tiempos de 2-3 min. Después, la mezcla de reacción se dejó calentar hasta t.a. y se agitó a esta temperatura durante 2.5 hr. Se añadió bromomalonato de dietilo adicional (1.08 ml, 1.6 mmoles) y la mezcla de reacción se agitó durante una hora más. El solvente se removió, se añadió agua y se extrajo con EtOAc. El crudo se purificó por cromatografía (cartucho de sílice, ciclohexano:EtOAc 95:5) para dar el compuesto del título (1.07 g).

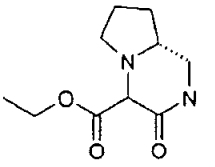
EM: m/z= 393 (M+1) y 415 (M+Na)

UPLC/MS: m/z= 393 (M+1) a t=0.79 min

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.25-7.45 (m, 5 H) 7.08-7.23 (m, 1H) 4.91-5.06 (m, 2H) 4.40-4.50 (m, 1H) 3.93-4.23 (m, 4 H) 2.94-3.14 (m, 3 H) 2.70-2.90 (m, 2H) 1.45-1.89 (m, 4 H) 1.07-1.28 (m, 6 H)

DESCRIPCION 111

(8a*R*)-3-oxooctahidropirrolo[1,2-a]pirazina-4-carboxilato de etilo (D111)



La solución de {(2*R*)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidinil}propanodioato de dietilo (D110, 1.07 g, 2.72 mmoles) en EtOH (aprox. 20 ml) se desgasificó, se añadió (10%) Pd/C (580 mg) y la mezcla de reacción se agitó bajo una atmósfera de H_2 durante 2.5 hr. El catalizador se filtró y el volumen de la solución filtrada se redujo bajo vacío. La solución se calentó a 50°C y se agitó a esta temperatura durante 6 hr y a temperatura ambiente durante 12 hr. El solvente se evaporó a sequedad para dar el compuesto del título (617 mg) como una mezcla de diaestereoisómeros (relación aprox. 70:30). Este crudo se usó en el siguiente paso sin purificación adicional.

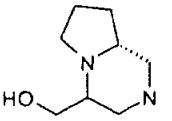
EM: m/z= 213 (M+1)

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.93-8.12 (m, 1H) 4.03-4.27 (m, 3 H) 3.15-3.30 (m, 1H) 2.91-3.07 (m, 1H) 2.77-2.93 (m, 1H) 2.37-2.47 (m, 1H) 2.03-2.15 (m, 1H) 1.63-1.94 (m, 3 H) 1.26-1.50 (m, 1H) 1.04-1.28 (m, 3 H)

La relación entre los dos diaestereoisómeros se determinó sobre la base de la relación integral de picos de diagnóstico tales como las señales de N-H lactama encontradas en el intervalo de 7.93-8.12.

DESCRIPCION 112

(8a*R*)-octahidropirrolo[1,2-*a*]pirazin-4-ilmetanol (D112)



A una solución de (8a*R*)-3-oxooctahidropirrolo[1,2-*a*]pirazina-4-carboxilato de etilo (D111, 207 mg, 0.976 mmoles) en THF (0.5 ml) se añadió $LiBH_4$ 2M en THF (1.46 ml) y la mezcla de reacción se puso a reflujo durante 17 hr. La mezcla de reacción se enfrió hasta t.a., se añadieron 9.7 ml de BH_3 1 M-THF y la mezcla se puso a reflujo durante 2 hr.

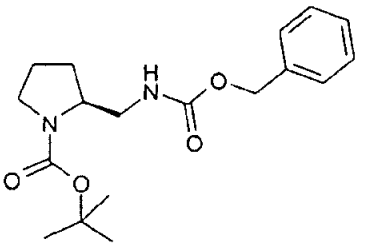
La mezcla de reacción se enfrió hasta 0°C y 4 ml de MeOH se añadieron. Después, 1.5 ml de HCl concentrado se añadieron a 0°C y la mezcla de reacción se puso a reflujo durante 1 hr. El solvente se evaporó a sequedad y el crudo se purificó por cartucho de SCX y después por cromatografía (sílice, CH_2Cl_2: NH_3 2M en MeOH 9:1 a 8:2) para dar el compuesto del título (73 mg) como ununa mezcla de diaestereoisómeros.

EM: m/z= 157 (M+1)

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 4.2-4.4 (m, 1H) 3.44-3.63 (m, 1H) 3.04-3.22 (m, 2H) 2.54-2.97 (m, 4 H) 2.05-2.31 (m, 1H) 1.84-2.03 (m, 1H) 1.40-1.85 (m, 3 H) 0.99-1.32 (m, 1H)

DESCRIPCION 113

(2*S*)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidincarboxilato de 1,1-dimetiletilo (D113)



A una solución de (*S*)-2-(aminometil)-1-N-Boc-pirrolidina (1.65 g, 8.25 mmoles) en 25 ml de diclorometano se añadió DIPEA (2.15 ml, 12.3 mmoles) y, a 0°C, cloroformiato de bencilo (1.41 ml, 9.9 mmoles). La mezcla de reacción se calentó hasta t.a. y después se agitó durante 3 hr a esta temperatura.

Se añadió salmuera a la mezcla de reacción, la capa acuosa se extrajo con diclorometano y las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (cartucho de sílice, ciclohexano: EtOAc 9:1) para dar el compuesto del título (2.23 g, rendimiento = 80%).

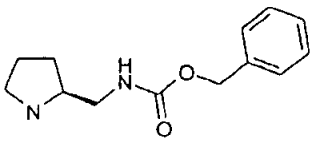
EM: m/z= 235 (M-BOC+1)

UPLC/MS: m/z= 235 (M-BOC+1); 335 (M+1) a t=0.8 min

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 6.98-7.49 (m, 6 H) 4.88-5.15 (m, 2H) 3.58-3.83 (m, 1H) 3.05-3.32 (m, 3 H) 2.75-3.04 (m, 1H) 1.52-1.98 (m, 4 H) 1.20-1.49 (m, 9 H)

DESCRIPCION 114

[(2S)-2-pirrolidinilmetil]carbamato de fenilmetilo (D114)



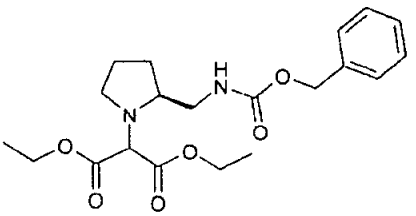
A una solución de (2*S*)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidincarboxilato de 1,1-dimetiletilo (D113, 2.23 g, 6.67 mmoles) en 16 ml de diclorometano, enfriada a 0°C, se añadieron 4 ml de TFA. La mezcla de reacción se dejó calentar hasta t.a. y después se agitó a esta temperatura durante 30 min. El compuesto del título se aisló como un aceite incoloro después de purificación por SCX (1.36 g).

EM: m/z= 235 (M-BOC+1)

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.04-7.47 (m, 6 H) 4.82-5.16 (m, 2H) 3.11-3.46 (m, 1H) 2.97-3.09 (m, 1H) 2.84-2.97 (m, 2H) 2.61-2.82 (m, 2H) 1.40-1.83 (m, 3 H) 1.10-1.37 (m, 1H)

DESCRIPCION 115

{(2S)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidinil} propanodioato de dietilo (D115)



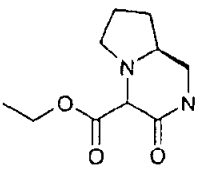
A una mezcla de [(2*S*)-2-pirrolidinilmetil]carbamato de fenilmetilo (D114, 1.36 g, 5.81 mmoles) y K_2CO_3 (1.6 g, 11.62 mmoles) en acetonitrilo (20 ml), enfriada a 0°C, se añadió gota a gota bromomalonato de dietilo (1.37 ml, 6.97 mmoles) en un tiempo de 2-3 min. Después, la mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 4 hr.

El volumen del solvente se redujo, se añadió salmuera y se extrajo con diclorometano. Las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (cartucho de sílice, ciclohexano: EtOAc 95:5 a 7:3) para dar el compuesto del título como un aceite incoloro (1.40 g, rendimiento =61 %).

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.23-7.48 (m, 5 H) 7.09-7.21 (m, 1H) 4.87-5.08 (m, 2H) 4.40- 4.50 (m, 1H) 3.98-4.23 (m, 4 H) 2.93-3.16 (m, 3 H) 2.62-2.91 (m, 2H) 1.43-1.92 (m, 4 H) 1.00-1.30 (m, 6 H)

DESCRIPCION 116

(8a*S*)-3-oxooctahidropirrolo[1,2-a]pirazina-4-carboxilato de etilo (D116)



La solución de {(2*S*)-2-[({[(fenilmetil)oxi]carbonil}amino)metil]-1-pirrolidinil}propanodioato de dietilo (D115, 1.40 g, 3.67 mmoles) en EtOH (aprox. 20 ml) se desgasificó, se añadió (10%) Pd/C (778 mg, 0.734 mmoles) y la mezcla de reacción se agitó bajo una atmósfera de H_2 durante 2.5 hr. El

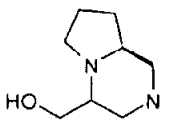
catalizador se filtró y el volumen de la solución filtrada se redujo bajo vacío. La solución se calentó a 50°C y se agitó a esta temperatura durante 7 hr. El solvente se evaporó a sequedad para dar el compuesto del título como un aceite amarillento (793 mg) como una mezcla de diaestereoisómeros. Este crudo se usó en el siguiente paso sin purificación adicional.

EM: m/z= 213 (M +1)

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.90-8.11 (m, 1H) 4.02-4.43 (m, 3 H) 3.15-3.30 (m, 1H) 2.79-3.07 (m, 2H) 2.36-2.56 (m, 1H) 2.0-2.2 (m, 1H) 1.63-2.18 (m, 3 H) 1.26-1.51 (m, 1H) 1.13-1.27 (m, 3 H)

DESCRIPCION 117

(8a*S*)-octahidropirrolo[1,2-*a*]pirazin-4-ilmetanol (D117)



A una solución de (8a*S*)-3-oxooctahidropirrolo[1,2-*a*]pirazina-4-carboxilato de etilo (D116, 403 mg, 1.88 mmoles) en THF (aprox. 3 ml) se añadió $LiBH_4$ 2M en THF (1.41 ml, 2.83 mmoles) y la mezcla de reacción se puso a reflujo durante la noche. La mezcla de reacción se enfrió hasta t.a., 18.8 ml de BH_3 1 M-THF se añadieron y la mezcla se puso a reflujo durante 2 hr.

La mezcla de reacción se enfrió a 0°C y se añadieron 8 ml de MeOH. Después, 3 ml de HCl concentrado se añadieron y la mezcla de

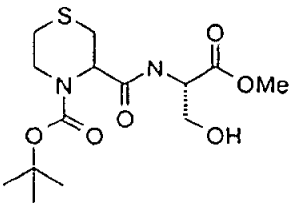
reacción se puso a reflujo durante aprox. 2 hr. Los solventes se evaporaron a sequedad y el crudo se purificó por SCX para dar el compuesto del título como un aceite incoloro (220 mg). Es una mezcla de diaestereoisómeros.

EM: m/z= 157 (M +1)

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 4.29-4.47 (m, 1H) 3.46-3.64 (m, 1H) 3.10-3.45 (m, 2H) 2.82-2.96 (m, 1H) 2.50-2.81 (m, 3 H) 1.44-2.38 (m, 5 H) 1.01-1.31 (m, 1H)

DESCRIPCION 118

3-({[(1S)-1-(hidroximetil)-2-(metiloxi)-2-oxoetil]amino}carbonil)-4-tiomorfolincarboxilato de 1,1-dimetiletilo (D118)



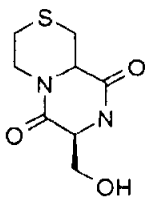
A una solución de ácido tiomorfolincarboxílico de N-Boc (1.36 g, 5.51 mmoles) en diclorometano (13.6 ml) se añadieron bajo N_2, a t.a., TBTU (1.95 g, 6.06 mmoles) y DIPEA (1.92 ml, 11.02 mmoles) y la solución se agitó durante 30 min. A una suspensión de clorhidrato de éster L-serinmetílico (1.71 g, 11.02 mmoles) en diclorometano (13.6 ml) se añadió DIPEA (1.92 ml, 11.02 mmoles) y la solución resultante se agitó durante 30 min. Después, la solución que contenía la base libre de serina se añadió a la mezcla de reacción y se dejó agitar durante 16 hr. Se añadió agua a la mezcla de reacción y la capa

acuosa se extrajo con diclorometano (x3) y las fases orgánicas combinadas se secaron (Na_2SO_4) y se evaporaron a sequedad. El compuesto del título crudo (3.87 g) se usó en el siguiente paso sin purificación adicional.

UPLC/MS: m/z= 371 (M+Na); 349 (M+1); 293 (M-*t*Bu); 249 (M-BOC+1) a t=0.59 min

DESCRIPCION 119

(7*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]tiazin-6,9-diona (D119)



A una solución del 3-({[(1*S*)-1-(hidroximetil)-2-(metiloxi)-2-oxoetil]amino}carbonil)-4-tiomorfolincarboxilato de 1,1-dimetiletilo crudo (D118, 3.87 g) en 44 ml de diclorometano se añadieron bajo N_2, a t.a., 22 ml de TFA. La mezcla de reacción se agitó a temperatura ambiente durante 3 hr. Los solventes se removieron bajo presión reducida y el residuo se purificó sobre un cartucho de SCX. La fracción eluida con amoniaco metanólico 2M se evaporó a sequedad y el residuo se disolvió en MeOH y se puso a reflujo durante 20 hr.

La mezcla de reacción se evaporó a sequedad y el producto deseado se purificó por SCX, eluyendo con MeOH. El compuesto del título (1.1 g, rendimiento = 92% en 2 pasos) se aisló como una mezcla de

diaestereoisómeros (relació ~ 50/50).

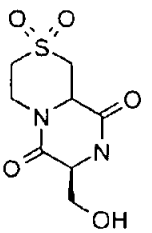
UPLC/MS: 1er pico m/z= 217 (M+1) a t=0.35 min; 2do. pico m/z= 217 (M+1) a t=0.36 min

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.07-8.31 (m, 1H) 4.62-4.82 (m, 1H) 3.95-4.18 (m, 1H) 3.69-3.95 (m, 2H) 3.30-3.66 (m, 2H) 2.85-3.02 (m, 1H) 2.69-2.86 (m, 2H) 2.52-2.68 (m, 1H).

La relación entre los dos diaestereoisómeros se determinó sobre la base de la relación integral de picos de diagnóstico tales como las señales de N-H lactama encontradas en el intervalo de 8.07-8.31.

DESCRIPCION 120

2,2-Dióxido de (7*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]tiazin-6,9-diona (D120)



A una suspensión de (7*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]tiazin-6,9-diona (D119, 1.1 g, 5.09 mmoles) en diclorometano (22 ml) se añadió a t.a. m-CPBA al 77% (2.85 g, 12.73 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 2 hr. El solvente se removió bajo presión reducida y el crudo se purificó por cromatografía (sílice, CH_2Cl_2: NH_3 2M en MeOH 98:2 a 8:2) para dar el compuesto del título como un sólido

blanco (900 mg, rend = 71%) como una mezcla de diaestereoisómeros (relación ~ 60/40).

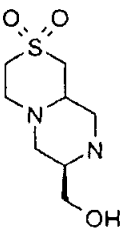
EM: m/z= 249 (M+1) y 271 (M+Na)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.29-8.54 (m, 1H) 5.02-5.59 (m, 1H) 4.59-4.89 (m, 1H) 4.16-4.47 (m, 1H) 3.86-3.99 (m, 1H) 3.69-3.86 (m, 1H) 3.50-3.68 (m, 1H) 3.21-3.48 (m, 3 H) 2.91-3.20 (m, 2H)

La relación entre los dos diaestereoisómeros se determinó sobre la base de la relación integral de picos de diagnóstico tales como las señales de O-H alcohol encontradas en el intervalo de 5.02-5.59.

DESCRIPCION 121

[(7*R*)-2,2-dioxidooctahidropirazino[2,1-*c*][1,4]tiazin-7-il]metanol (D121)



A una suspensión de 2,2-dióxido de (7*S*)-7-(hidroximetil) hexahidropirazino[2,1-*c*][1,4]tiazin-6,9-diona (D120, 900 mg, 3.63 mmoles) en THF (10 ml) se añadieron bajo N_2, a t.a., 36.3 ml de solución de BH_3-THF 1M. La mezcla de reacción se puso a reflujo durante 16 hr. Se añadió HCl 6N (20 ml) a la mezcla de reacción, enfriada a 0°C, y la mezcla resultante se puso a reflujo durante 2 hr. Después, la mezcla de reacción se evaporó a sequedad y el crudo se purificó por SCX para dar el compuesto del título como una

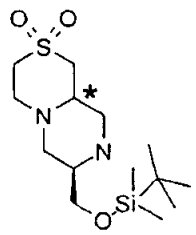
espuma blanca (753 mg, rendimiento = 94%)

EM: m/z= 221 (M+1) y 243 (M+Na)

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 4.40-4.63 (m, 1H) 3.33-3.48 (m, 1H) 2.95-3.27 (m, 4 H) 2.72-2.95 (m, 3 H) 2.53-2.72 (m, 2H) 2.20-2.41 (m, 2H) 1.98-2.18 (m, 1H) 1.65-1.85 (m, 1H).

DESCRIPCION 122 y 123

2,2-Dióxido de (7*R*,9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil) octahidropirazino[2,1-*c*][1,4]tiazina (DESCRIPCION 122- diaestereoisómero 1) y 2,2-dióxido de (7*R*, 9a*S* o 9a*R*)-7-({[(1,1-dimetiletil) (dimetil)silil]oxi}metil)octahidropirazino[2,1-c][1,4]tiazina (DESCRIPCION 123- diaestereoisómero 2)



A una suspensión de [(7*R*)-2,2-dioxidooctahidropirazino[2,1-*c*][1,4]tiazin-7-il]metanol (D121, 753 mg, 3.42 mmoles) en diclorometano (30 ml) se añadieron a t.a. Et_3N (1.9 ml, 13.68 mmoles) y TDBMSCl (1.5 g, 10.3 mmoles). La mezcla de reacción se agitó durante 16 hr a t.a.

$NaHCO_3$ saturado se añadió y la fase acuosa se extrajo con diclorometano (x3) y las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice,

CH_2Cl_2:MeOH 1:0 a 97:3) para los compuestos de título:

D122- Diaestereoisómero 1 (566 mg, aceite incoloro):

EM: m/z= 335 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 3.47-3.66 (m, 2H) 2.99-3.27 (m, 3 H) 2.80-2.95 (m, 3 H) 2.67-2.80 (m, 3 H) 2.56-2.66 (m, 2H) 2.21-2.34 (m, 1H) 0.55-1.1 1 (s, 9 H) -0.23-0.26 (s, 6 H)

D123- Diaestereoisómero2 (382 mg, sólido blanco):

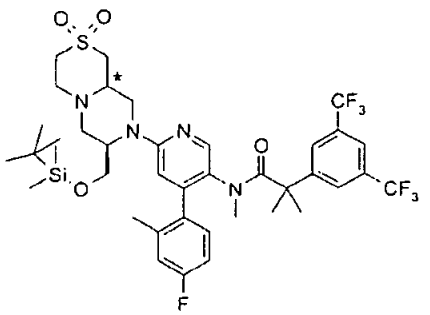
EM: m/z= 335 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 3.39-3.48 (m, 1H) 3.31-3.40 (m, 1H) 3.13 (t, 1H) 2.91-3.09 (m, 3 H) 2.70-2.85 (m, 3 H) 2.56-2.65 (m, 1H) 2.42-2.51 (m, 1H) 2.19-2.36 (m, 2H) 1.91-2.06 (m, 1H) 1.74 (t, 1H) 0.80 (s, 9 H) -0.02 (s, 6 H)

DESCRIPCION 124

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*R*, 9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida

(D124- diaestereoisómero 1)



A una solución de 2,2-dióxido de (7*R*, 9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]tiazina (D122, 120 mg, 0.36 mmoles) en 2.2 ml de tolueno se añadieron 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (147 mg, 0.28 mmoles), bis-tri-ter-butilfosfinopaladio (29 mg), cloruro de hexadeciltrimetilamonio (17.8 µl de una solución acuosa al 25%) y solución de hidróxido de sodio (36 µl de una solución acuosa al 50%). La mezcla de reacción se desgasificó por ciclos de congelamiento-bombeo-descongelamiento y después se agitó a 90°C durante 4 hr.

EtOAc y $NaHCO_3$ ac. saturado se añadieron a la mezcla de reacción y la fase acuosa se extrajo con EtOAc (x3). Las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice, ciclohexano: EtOAc 7:3 a 0:1) para dar el compuesto del título como un sólido blanco (201 mg).

CLAR/EM: m/z= 831 (M+1) a t=4.56 min

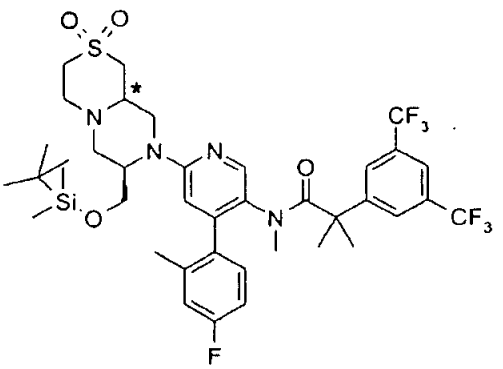
EM: m/z= 831 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.86 (s, 1H) 7.63-7.81 (m, 2H) 6.95-7.21 (m, 3 H) 6.64 (s, 1H) 4.29-4.66 (m, 1H) 3.99-4.24 (m, 1H) 3.78-3.95 (m, 1H) 3.59-3.81 (m, 1H) 3.08-3.26 (m, 3 H) 2.91-3.16 (m, 3 H) 2.63-2.87 (m, 1H) 2.48 (s, 3 H) 2.37-2.60 (m, 2H) 2.08-2.33 (m, 1H) 2.09 (s, 3 H) 1.37 (s, 6 H) 0.77 (s, 9 H) 0.01 (s, 6 H)

DESCRIPCION 125

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*R*, 9a*S* o 9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida

(D125- Diaestereoisómero 2)



A una solución de 2,2-dióxido de (7*R*, 9a*S* o 9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]tiazina (D123, 120 mg, 0.36 mmoles) en 2.2 ml de tolueno se añadieron 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (147 mg, 0.28 mmoles), bis-tri-ter-butilfosfinopaladio (29 mg), cloruro de hexadeciltrimetilamonio (18 µl de una solución acuosa al 25%) y solución de hidróxido de sodio (36 µl de una solución acuosa al 50%). La mezcla de reacción se desgasificó por ciclos de congelamiento-bombeo-descongelamiento y se agitó a 90°C durante 5 hr. Después, bis-tri-ter-butilfosfinopaladio adicional (29 mg) se añadió y la mezcla de reacción se agitó a 90°C durante una hora más y se dejó en congelamientor durante la noche.

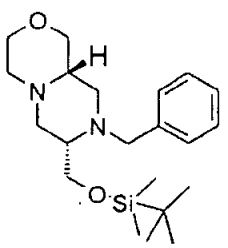
EtOAc y $NaHCO_3$ ac. saturado se añadieron a la mezcla de reacción y la fase acuosa se extrajo con EtOAc (x3). Las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice, ciclohexano: EtOAc 7:3 a 0:1) para dar el compuesto del título como un sólido blanco (127.4 mg, rendimiento =55%).

EM: m/z= 831 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.86 (s, 1H) 7.60-7.82 (m, 2H) 7.16 (d, 1H) 6.98-7.14 (m, 2H) 6.67 (s, 1H) 4.36-4.54 (m, 1H) 3.91-4.12 (m, 1H) 3.80-3.94 (m, 1H) 3.58-3.73 (m, 1H) 3.08-3.47 (m, 5 H) 2.87-3.00 (m, 1H) 2.72-2.82 (m, 1H) 2.42-2.67 (m, 6 H) 2.13-2.25 (m, 5 H) 1.26-1.54 (m, 4 H) 0.78 (s, 9 H) 0.00 (s, 6 H)

DESCRIPCION 126

(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-8-(fenilmetil) octahidropirazino[2,1-*c*][1,4]oxazina (D126)



A una solución de (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil) silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D 22, 200 mg, 0.7 mmoles) en dicloroetano (3 ml) se añadieron bajo N_2, a t.a., PhCHO (0.142 ml, 1.4 mmoles) y AcOH (79 µl, 1.4 mmoles) y la mezcla de reacción se agitó durante

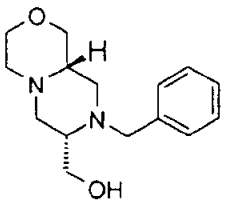
30 min. Se añadió triacetoxiborhidruro de sodio (295 mg, 1.4 mmoles) y la mezcla de reacción se agitó durante 3.5 hr. $NaHCO_3$ ac. se añadió a la mezcla de reacción y las dos fases se separaron. La fase acuosa se extrajo con diclorometano (3X) y las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por SCX y por cromatografía (sílice, CH_2Cl_2:NH_3 2M en MeOH 1:0 a 95:5) para dar 276 mg del compuesto del título como un aceite incoloro (276 mg, rendimiento =cuantitativo)

UPLC/MS: m/z= 377 (M+1) a t=0.69 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.27-7.32 (m, 4 H) 7.18-7.24 (m, 1H) 3.94 (t, 1H) 3.83 (d, 1H) 3.78-3.89 (m, 1H) 3.68-3.75 (m, 1H) 3.65 (d, 1H) 3.42-3.54 (m, 2H) 3.02 (t, 1H) 2.74 (dd, 2H) 2.45-2.50 (m, 1H) 2.18-2.32 (m, 3 H) 2.08-2.18 (m, 2H) 0.84 (s, 9 H) 0.02 (s, 3 H) 0.00 (s, 3 H)

DESCRIPCION 127

[(7*S*,9a*S*)-8-(fenilmetil)octahidropirazino[2,1-*c*][1,4]oxazin-7-il]metanol (D127)



A una solución de (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil) silil]oxi}metil)-8-(fenilmetil)octahidropirazino[2,1-*c*][1,4]oxazina (D126, 276 mg, 0.73 mmoles) en MeOH (24 ml), enfriada a 0°C, se añadió gota a gota HCl

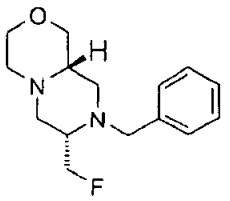
12N (1.4 ml). La mezcla de reacción se agitó durante 2 hr a t.a., después se puso en el congelador durante 12 hr. La mezcla de reacción se calentó hasta t.a., HCl adicional se añadió (0.7 ml) y la mezcla de reacción se agitó durante 2 hr más. La mezcla se filtró sobre un cartucho de SCX lavando con metanol y después con amoniaco metanólico 2M. Las fracciones eluidas con amoniaco se combinaron y se evaporaron a sequedad para dar el compuesto del título como un aceite incoloro (150 mg, rendimiento = 78%).

UPLC/MS: m/z= 263 (M+1) a t=0.41 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.26-7.33 (m, 4 H) 7.19-7.24 (m, 1H) 4.42 (br. s., 1H) 3.81 (d, 1H) 3.74-3.83 (m, 2H) 3.60-3.72 (m, 2H) 3.43-3.52 (m, 2H) 3.02 (t, 1H) 2.78 (d, 1H) 2.64-2.72 (m, 1H) 2.53 (dd, 1H) 2.18-2.29 (m, 3 H) 2.08-2.17 (m, 2H)

DESCRIPCION 128

(7*S*,9a*S*)-7-(fluorometil)-8-(fenilmetil)octahidropirazino[2,1-*c*][1,4]oxazina (D128)



A una solución de [(7*S*,9a*S*)-8-(fenilmetil)octahidropirazino[2,1-*c*][1,4]oxazin-7-il]metanol (D127, 125 mg, 0.477 mmoles) en diclorometano (5 ml), enfriada a -78°C, se añadió DAST (0.187 ml, 1.431 mmoles) gota a gota y

la mezcla de reacción se agitó durante 16 hr dejando que la temperatura se incrementara a t.a. Se añadió agua a la mezcla de reacción y las dos fases se separaron. La fase acuosa se extrajo con diclorometano (3X) y las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice, CH_2Cl_2:MeOH 1:0 a 96:4) para dar el compuesto del título (106 mg).

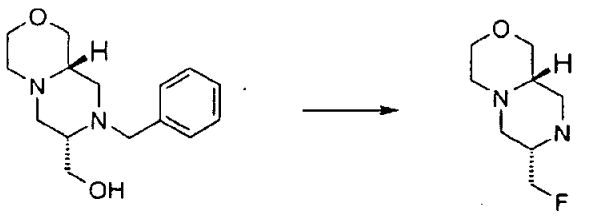
EM: m/z= 265 (M+1)

UPLC/MS: m/z= 265 (M+1) a t=0.47 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.26-7.34 (m, 4 H) 7.19-7.26 (m, 1H) 4.82-4.99 (m, 1H) 4.59-4.76 (m, 1H) 3.85 (d, 1H) 3.70 (dd, 1H) 3.63 (d, 1H) 3.50 (dd, 1H) 3.43-3.51 (m, 1H) 3.02-3.09 (m, 1H) 3.03 (t, 1H) 2.68 (d, 1H) 2.54 (d, 1H) 2.29-2.36 (m, 2H) 2.24 (t, 1H) 2.08-2.16 (m, 2H)

DESCRIPCION 129

(7*S*,9a*S*)-7-(fluorometil)octahidropirazino[2,1-*c*][1,4]oxazina (D129)



A una solución de (7*S*,9a*S*)-7-(fluorometil)-8-(fenilmetil) octahidropirazino[2,1-*c*][1,4]oxazina (D128, 30 mg, 0.11 mmoles) en AcOH (30 ml) se añadió negro de Pd (12 mg, 0.11 mmoles) y la mezcla de reacción se agitó bajo una atmósfera de H_2 (5 atm.) durante 1.5 hr. La mezcla de reacción

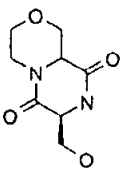
se filtró sobre un cartucho de SCX lavando con metanol y después con amoniaco metanólico 2M. Las fracciones eluidas con amoniaco se combinaron y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice, CH_2Cl_2:MeOH 1:0 a 8:2) para dar el compuesto del título (14.9 mg, rendimiento = 78%).

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 4.55-4.65 (m, 1H) 4.42-4.53 (m, 1H) 3.65 (dd, 1H) 3.38-3.53 (m, 2H) 2.99 (t, 1H) 2.93-3.01 (m, 1H) 2.58 (dd, 1H) 2.42-2.45 (m, 1H) 2.37 (dd, 1H) 2.28-2.37 (m, 1H) 2.12-2.20 (m, 1H) 2.02-2.11 (m, 1H) 1.92-2.00 (m, 1H)

El patrón de pico cruzado de ROESY es de conformidad con una estereoquímica relativa syn.

DESCRIPCION 130

(7*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazina-6,9-diona (D130)



Acido *N*-Boc-3-morfolincarboxílico (1.038 g, 4.49 mmoles) se suspendió en diclorometano anhidro (20 ml). A este se añadió EDC (1.3 g, 6.78 mmoles) y HOBt (607 mg, 4.49 mmoles) y se agitó durante 30 minutos a T.A., tiempo en el cual se observó la disolución completa del material de partida. Se añadió una solución de clorhidrato de éster L-Ser-metílico (1.10 g, 17.07 mmoles), y DIPEA (1.23 ml, 7.07 mmoles) en diclorometano seco (10

ml). La mezcla resultante se agitó durante la noche. Se diluyó con diclorometano (50 ml), se lavó con solución de $NaHCO_3$ saturada (2 x 50 ml) y salmuera (50 ml). Se secó (Na_2SO_4) y el solvente se removió bajo presión reducida para dar un crudo que se usó en el siguiente paso.

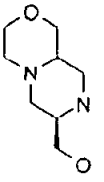
Este se disolvió en 20 ml de diclorometano y se trató con 10 ml de TFA. La reacción se detuvo después de 4 hr. La mezcla se hizo pasar a través de una columna SCX. Los componentes básicos se eluyeron con amoniaco metanólico 1M. El solvente se removió dejando un residuo oleoso, que se volvió a disolver en MeOH y se calentó para remover el solvente. Se formó un precipitado, que se recogió por filtración como un sólido blanco, correspondiente al compuesto del título, con un exceso diaestereomérico de 70:30.

EM (directo): m/z= 201 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.15 (br. s., 1H) 5.16 (t, 1H) 4.22 (dd, 1H) 4.08-4.13 (m, 1H) 4.00 (dd, 1H) 3.84-3.88 (m, 1H) 3.77-3.83 (m, 1H) 3.71-3.80 (m, 1H) 3.44-3.51 (m, 1H) 3.41 (t, 1H) 3.30 (t, 1H) 2.77 (td, 1H) (mezcla de diaestereoisómeros, relación de aproximadamente 70:30)

DESCRIPCION 131

(7*R*)-octahidropirazino[2,1-*c*][1,4]oxazin-7-ilmetanol (D131)

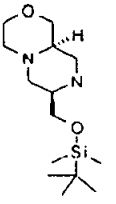


(7*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazina-6,9-diona (D130, 151 mg, 0.75 mmoles) se suspendió en solución de complejo de borano-THF 1M (7.5 ml) y se calentó a reflujo durante 24 horas. Se verificó por EM, que mostró sólo el producto a m/z= 173 (M+1). La reacción se enfrió a 0°C, se añadió gota a gota MeOH (5 ml) seguido por solución de HCl concentrada (1 ml). La mezcla resultante se calentó a 50°C durante 4 horas. El solvente se removió y el residuo se cargó en una columna SCX, se lavó con MeOH antes de eluir el compuesto con NH_3 1 M en MeOH. El solvente se evaporó bajo presión reducida para dar el compuesto del título como un aceite incoloro (125 mg).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 4.43 (t, 1H) 3.68 (dd, 1H) 3.62 (t, 1H) 3.40-3.58 (m, 4 H) 3.02 (t, 1H) 2.66-2.74 (m, 1H) 2.62 (d, 1H) 2.42-2.51 (m, 1H) 2.31-2.39 (m, 1H) 2.15 (dd, 1H) 2.09 (td, 1H) 1.92-2.03 (m, 1H)

DESCRIPCION 132

(7*R*,9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina



(7*R*)-octahidropirazinó[2,1-*c*][1,4]oxazin-7-ilmetanol (D131, 93 mg, 0.54 mmoles, una muestra recuperada de un intento fallido en la sililación

de la preparación de Dnn) se disolvió en diclorometano seco (2 ml) y se trató con Et_3N (0.15 ml, 1.08 mmoles), y TBDMS-Cl (122 mg, 0.81 mmoles). La mezcla de reacción resultante se agitó durante la noche a T.A. Esta se verificó por EM directa, no mostrando material de partida, se colocó en el pico esperado a m/z= 287 (M+1 del producto). Se diluyó con diclorometano (20 ml) y se lavó con solución de $NaHCO_3$ saturada (2 x 2O ml), se secó (Na_2SO_4) y el solvente se removió. El residuo se purificó por cromatografía instantánea (sílice, diclorometano a diclorometano: MeOH 90:10), dejando el producto como un aceite claro.

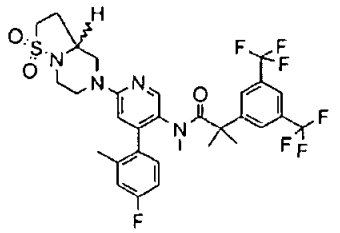
EM (directo): m/z= 287 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.48 (br. s., 1H) 7.07 (br. s., 1H) 3.82 (dd, 1H) 3.75 (dd, 1H) 3.69 (dd, 1H) 3.55 (dd, 1H) 3.42-3.49 (m, 1H) 3.03 (t, 1H) 2.86-2.93 (m, 1H) 2.68 (dd, 1H) 2.50-2.54 (m, 1H) 2.33-2.46 (m, 2H) 2.21 (dd, 1H) 2.04-2.16 (m, 2H) 0.86 (s, 9 H) 0.04 (s, 6 H) - forma protonada.

EJEMPLO 1

2-[3,5-Bis(trifluorometil)fenil]-*N*-[6-(1,1-dioxidohexahidro-5*H*-isotiazol[2,3-*a*]pirazin-5-il)-4-(4-fluoro-2-metilfenil)piridin-3-il]-*N*,2-dimetilpropanamida

(E1)



Un vial sellado de 8 ml se cargó con 100 mg (0.187 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 98 mg (0.561 mmoles) de 1,1-dióxido de hexahidro-2*H*-isotiazol[2,3-*a*]pirazina (D10), 52 mg (0.374 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 180°C durante 36-48 hr y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con diclorometano; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a ciclohexano/acetato de etilo 1:1 y dando 44 mg (0.065 mmoles) del compuesto del título como sólido amarillo pálido.

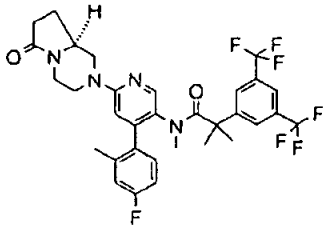
EM (ES/+): 673 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.08-6.85 (m, 3H); 6.53 (s, 1H); 4.81-4.53 (m, 1H); 4.35-4.09 (m, 1H); 3.53-3.50 (m, 1H); 3.38-3.25 (m, 1H); 3.16-3.09 (m, 1H); 2.96 (t, 1H); 2.83 (t, 1H);

2.70-1.98 (m, 10H); 1.79-1.47 (m, 3H); 1.46-1.33 (s, 3H).

EJEMPLO 2

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*S*)-6-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E2)



Un vial sellado de 8 ml se cargó con 100 mg (0.187 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 78.6 mg (0.561 mmoles) de (8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-6(2H)-ona (WO 2003/066635), 52 mg (0.374 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 180°C durante 36-48 hr y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con diclorometano; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 52 mg del compuesto del título como sólido amarillo pálido.

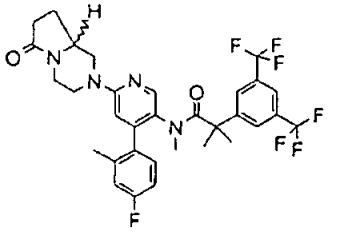
EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H);

7.05-6.87 (m, 3H); 6.52 (s, 1H); 4.67-4.52 (m, 1H); 4.32-4.19 (m, 1H); 4.14-4.10 (d, 1H); 3.77-3.64 (m, 1H); 3.02- 2.84 (m, 2H); 2.61 (t, 1H); 2.48-2.44 (dd, 2H); 2.41-2.33 (s, 3H); 2.30-2.22 (m, 1H); 2.13 (s, 3H); 1.79-1.65 (m, 1H); 1.53 (s, 3H); 1.38 (s, 3H).

EJEMPLO 3

2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(6-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E3)



Un vial sellado de 8 ml se cargó con 100 mg (0.187 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 78.6 mg (0.561 mmoles) de hexahidropirrolo[1,2-*a*]pirazin-6(2H)-ona (WO 2003/066635), 52 mg (0.374 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 180°C durante 36-48 hr y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con diclorometano; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 71 mg del compuesto del título como sólido amarillo

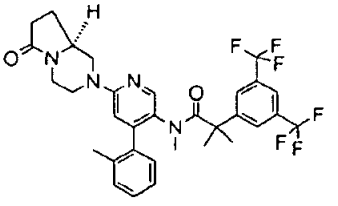
pálido.

EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.05-6.87 (m, 3H); 6.52 (s, 1H); 4.67-4.52 (m, 1H); 4.32-4.19 (m, 1H); 4.14-4.10 (d, 1H); 3.77-3.64 (m, 1H); 3.02-2.84 (m, 2H); 2.61 (t, 1H); 2.48-2.44 (dd, 2H); 2.41-2.33 (s, 3H); 2.30-2.22 (m, 1H); 2.13 (s, 3H); 1.79-1.65 (m, 1H); 1.53 (s, 3H); 1.38 (s, 3H)

EJEMPLO 4

2-[3,5-Bis(trifluorometil)fenil]-*N*,2-dimetil-N-{4-(2-metilfenil)-6-[(8a*S*)-6-oxohexahidropirrolo[1,2-*a*]pirazin-2(1H)-il]-3-piridinil}propanamida (E4)



Un vial sellado de 8 ml se cargó con 100 mg (0.161 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 67 mg (0.483 mmoles) de (8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-6(2*H*)-ona (WO 2003/066635), 44.5 mg (0.322 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 180°C durante 36-48 hr y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo

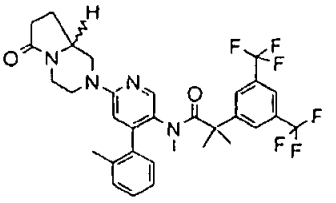
con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 56 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 619 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.07-8.00 (m, 1H); 7.81-7.77 (m, 1H); 7.73-7.63 (m, 2H); 7.37- 7.21 (m, 4H); 6.61-6.56 (m, 1H); 4.68-4.54 (m, 1H); 4.33-4.19 (m, 1H); 4.18-4.08 (d, 1H); 3.78-3.67 (m, 1H); 3.04-2.85 (m, 2H); 2.69-2.54 (t, 1H); 2.53-2.42 9dd, 1H); 2.42-2.33 (m, 3H); 2.33-2.23 (m, 1H); 2.21-2.10 (m, 3H); 1.78-1.66 (m, 1H); 1.57-1.48 (m, 3H); 1.42-1.32 (m, 3H).

EJEMPLO 5

2-[3,5-Bis(trifluorometil)fenil]-*N*,2-dimetil-*N*-[4-(2-metilfenil)-6-(6-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il)-3-piridinil]propanamida (E5)



Un vial sellado de 8 ml se cargó con 100 mg (0.161 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 67 mg (0.483 mmoles) de hexahidropirrolo[1,2-*a*]pirazin-6(2H)-ona (WO 2003/066635), 44.5 mg (0.322 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 180°C durante 36-48 hr y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con

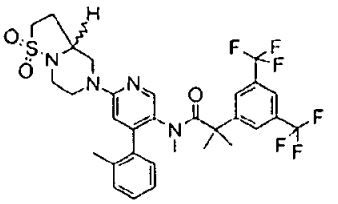
DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 45 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 619 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.07-8.00 (m, 1H); 7.81-7.77 (m, 1H); 7.73-7.63 (m, 2H); 7.37-7.21 (m, 4H); 6.61-6.56 (m, 1H); 4.68-4.54 (m, 1H); 4.33-4.19 (m, 1H); 4.18-4.08 (d, 1H); 3.78-3.67 (m, 1H); 3.04-2.85 (m, 2H); 2.69-2.54 (t, 1H); 2.53-2.42 9dd, 1H); 2.42-2.33 (m, 3H); 2.33-2.23 (m, 1H); 2.21-2.10 (m, 3H); 1.78-1.66 (m, 1H); 1.57-1.48 (m, 3H); 1.42-1.32 (m, 3H).

EJEMPLO 6

2-[3,5-Bis(trifluorometil)fenil]-*N*-[6-(1,1-dioxidohexahidro-5*H*-isotiazol[2,3-*a*]pirazin-5-il)-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E6)



El compuesto del título se preparó empezando a partir de 100 mg (0.161 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 85 mg (0.483 mmoles) de 1,1-dióxido de hexahidro-2*H*-isotiazol[2,3-*a*] pirazina (D10), 44.5 mg (0.322 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 180°C durante 36-48 hr y después

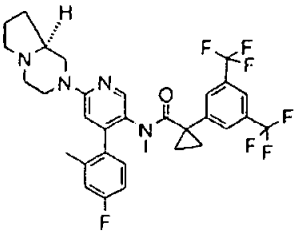
se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a ciclohexano/acetato de etilo 1:1 y dando 80 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 655 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.08-8.00 (m, 1H), 7.82-7.76 (m, 1H); 7.71-7.64 (m, 2H); 7.37-7.22 (m, 4H); 6.62-6.57 (m, 1H); 4.80-4.60 (m, 1H); 4.36-4.12 (m, 1H); 3.58-3.46 (m, 1H); 3.39-3.27 (m, 1H); 3.25-3.16 (m, 1H); 3.17-3.08 (t, 1H); 3.05-2.91 (t, 1H); 2.90-2.78 (t, 1H); 2.54-2.44 (m, 3H); 2.44-2.31 (m, 2H); 2.20-2.12 (m, 3H); 2.31-2.01 (m, 1H); 1.58-1.50 (m, 3H); 1.44-1.31 (m, 3H)

EJEMPLO 7

1-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-2(1H)-il]-3-piridinil}-*N*-metilciclopropan-carboxamida (E7)



El compuesto del título se preparó empezando a partir de 100 mg (0.188 mmoles) de 1-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]ciclopropancarboxamida (D2), 70 mg (0.554 mmoles) de

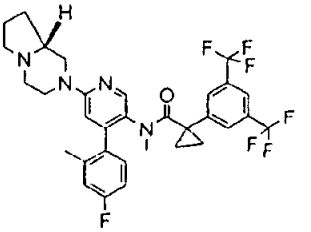
(8a*S*)-octahidropirrolo[1,2-*a*]pirazina, 52.2 mg (0.377 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 150°C durante la noche y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con diclorometano; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 1:1, a 100% de acetato de etilo, dando 72 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 621 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 7.93-7.89 (s, 1H); 7.86-7.82 (s, 1H); 7.67-7.62 (s, 2H); 7.06-7.01 (d, 1H); 6.89-6.77 (m, 2H); 6.57-6.52 (m, 1H); 4.38-4.34 (d, 1H); 4.21-4.17 (d, 1H); 3.10-2.87 (m, 2H); 2.88-2.84 (s, 3H); 2.62-2.50 (m, 1H); 2.26-2.06 (m, 2H); 2.17-2.10 (s, 3H); 2.06-1.94 (s, 1H); 1.90-1.61 (m, 3H); 1.46-1.10 (m, 6H)

EJEMPLO 8

1-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*-metilciclopropan-carboxamida (E8)



El compuesto del título se preparó empezando a partir de 100

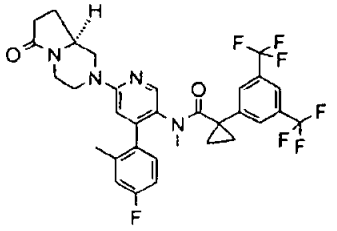
mg (0.188 mmoles) de 1-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]ciclopropancarboxamida (D2), 70 mg (0.554 mmoles) de (8a*R*)-octahidropirrolo[1,2-a]pirazina, 52.2 mg (0.377 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 150°C durante la noche y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 1:1, a 100% de acetato de etilo y dando 70 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 621 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 7.93-7.89 (s, 1H); 7.86-7.82 (s, 1H); 7.67-7.62 (s, 2H); 7.06-7.01 (d, 1H); 6.89-6.77 (m, 2H); 6.57-6.52 (m, 1H); 4.38-4.34 (d, 1H); 4.21-4.17 (d, 1H); 3.10-2.87 (m, 2H); 2.88-2.84 (s, 3H); 2.62-2.50 (m, 1H); 2.26-2.06 (m, 2H); 2.17-2.10 (s, 3H); 2.06-1.94 (s, 1H); 1.90-1.61 (m, 3H); 1.46-1.10 (m, 6H)

EJEMPLO 9

1-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*S*)-6-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*-metilciclopropan-carboxamida (E9)



El compuesto del título se preparó empezando a partir de 50 mg (0.094 mmoles) de 1-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]ciclopropancarboxamida (D2), 39 mg (0.278 mmoles) de (8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-6(2H)-ona (WO 2003/066635), 26.2 mg (0.189 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.4 ml de DMSO. La mezcla de reacción se calentó a 150°C durante la noche y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 1:1, a 100% de acetato de etilo y dando 26 mg del compuesto del título como sólido amarillo pálido.

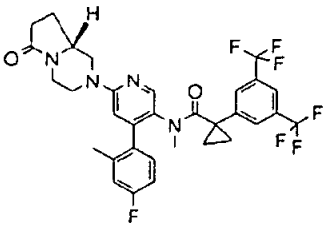
EM (ES/+): 635 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.03-7.99 (m, 1H); 7.99-7.95 (m, 1H); 7.74-7.69 (m, 2H); 7.20-7.10 (m, 1H); 7.06-6.93 (m, 1H); 6.92-6.83 (m, 1H); 6.81-6.74 (m, 1H); 4.55-4.47 (d, 1H); 4.44-4.37 (d, 1H); 3.88-3.78 (d, 1H);

3.60-3.50 (d, 1H); 2.84-2.66 (m, 4H); 2.59-2.38 (m, 2H); 2.32-2.18 (m, 2H); 2.15-2.09 (m, 3H); 2.17-2.06 (m, 1H); 1.64-1.53 (m, 1H); 1.32-1.19 (m, 2H); 1.15-1.02 (m, 1H); 0.96-0.78 (1, H).

EJEMPLO 10

1-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-6-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*-metilciclopropanocarboxamida (E10)



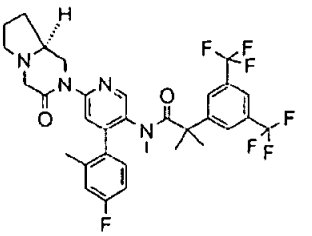
El compuesto del título se preparó a partir de 50 mg (0.094 mmoles) de 1-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]ciclopropancarboxamida (D2), 39 mg (0.278 mmoles) de (8a*R*)-hexahidropirrolo[1,2-*a*]pirazin-6(2*H*)-ona (WO 2003/066635), 26.2 mg (0.189 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.4 ml de DMSO. La mezcla de reacción se calentó a 150°C durante la noche y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 1:1, a 100% de acetato de etilo y dando 12 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 635 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.03-7.99 (m, 1H); 7.99-7.95 (m, 1H); 7.74-7.69 (m, 2H); 7.20-7.10 (m, 1H); 7.06-6.93 (m, 1H); 6.92-6.83 (m, 1H); 6.81-6.74 (m, 1H); 4.55-4.47 (d, 1H); 4.44-4.37 (d, 1H); 3.88-3.78 (d, 1H); 3.60-3.50 (d, 1H); 2.84-2.66 (m, 4H); 2.59-2.38 (m, 2H); 2.32-2.18 (m, 2H); 2.15-2.09 (m, 3H); 2.17-2.06 (m, 1H); 1.64-1.53 (m, 1H); 1.32-1.19 (m, 2H); 1.15-1.02 (m, 1H); 0.96-0.78 (1, H).

EJEMPLO 11

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*S*)-3-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E11)



El compuesto del título se preparó empezando a partir de 100 mg (0.187 mmoles) de 2-[3,5- bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 79 mg (0.563 mmoles) de (8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-3(4*H*)-ona (D12), 72 mg de yoduro de cobre (0.378 mmoles), 40 µl (0.375 mmoles) de *N,N*-dimetilmetanodiamina, 112.4 mg (0.375 mmoles) de carbonato de cesio; los reactivos se disolvieron en 4 ml de dioxano y se calentaron a 80°C durante 4 hr y después a 120°C durante la noche. El material crudo se purificó sobre

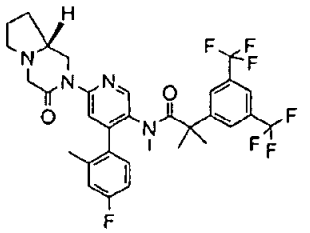
cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 54 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.39-8.23 (br. s, 1H), 8.09-7.97 (s, 1H), 7.87-7.64 (m, 3H), 7.21 (d, 1H), 7.17-7.06 (m, 2H), 4.62-4.15 (m, 2H), 4.09-3.65 (m, 2H), 3.19-3.00 (m, 1H), 2.87-2.53 (m, 2H), 2.42-2.24 (m, 1H), 2.20-2.04 (m, 6H), 2.00-1.88 (m, 1H), 1.88-1.76 (m, 1H), 1.75-1.59 (m, 1H), 1.59-1.47 (m, 1H), 1.46-1.23 (m, 6H)

EJEMPLO 12

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-3-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E12)



El compuesto del título se preparó empezando a partir de 100 mg (0.187 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 79 mg (0.563 mmoles) de (8a*R*)-hexahidropirrolo[1,2-*a*]pirazin-3(4H)-ona (D14), 72 mg de yoduro de cobre (0.378 mmoles), 40 µl (0.375 mmoles) de *N,N*-

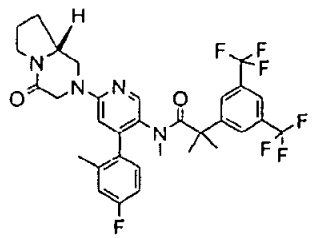
dimetilmetanodiamina, 112.4 mg (0.375 mmoles) de carbonato de cesio; los reactivos se disolvieron en 4 ml de dioxano y se calentaron a 80°C durante 4 hr y después a 120°C durante la noche. El material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 60 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.39-8.23 (br. s, 1H), 8.09-7.97 (s, 1H), 7.87-7.64 (m, 3H), 7.21 (d, 1H), 7.17-7.06 (m, 2H), 4.62-4.15 (m, 2H), 4.09-3.65 (m, 2H), 3.19-3.00 (m, 1H), 2.87-2.53 (m, 2H), 2.42-2.24 (m, 1H), 2.20-2.04 (m, 6H), 2.00-1.88 (m, 1H), 1.88-1.76 (m, 1H), 1.75-1.59 (m, 1H), 1.59-1.47 (m, 1H), 1.46-1.23 (m, 6H).

EJEMPLO 13

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-4-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E13)



El compuesto del título se preparó empezando a partir de 250 mg (0.47 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-

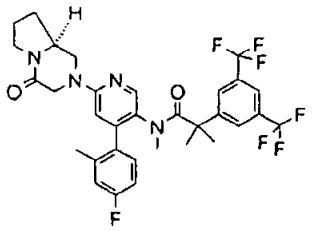
metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), (8a*R*)-hexahidropirrolo[1,2-*a*]pirazin-4(1*H*)-ona (D4), 164.4 mg (1.17 mmoles), 130 mg de carbonato de potasio (0.94 mmoles); los reactivos se disolvieron en 1.5 ml de DMSO. La mezcla de reacción se calentó a 150°C durante la noche y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 115 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.95-7.89 (s, 1H); 7.80-7.69 (br.s, 2H); 7.74-7.64 (br.s, 1H); 7.19-7.11 (d, 1H); 6.71-6.65 (s, 1H); 4.77-4.64 (d, 1H); 4.45-4.32 (d, 1H); 3.72-3.59 (m, 1H); 3.52-3.41 (dd, 1H); 3.39-3.31 (m, 1H); 2.83-2.73 (t, 1H); 2.60-2.50 (m, 1H); 2.31-2.17 (s, 3H); 2.21-2.15 (m, 1H); 2.15-2.05 (s, 3H); 1.97-1.88 (m, 1H); 1.82-1.71 (m, 1H); 1.71-1.58 (m, 1H); 1.55-1.42 (s, 3H); 1.41-1.27 (s, 3H).

EJEMPLO 14

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-4-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E14)



El compuesto del título se preparó empezando a partir de 135 mg (0.253 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 70 mg (0.5 mmoles) de (8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-4(1*H*)-ona (EP 300189), 70 mg (0.5 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 150°C durante la noche y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 24 mg del compuesto del título como sólido amarillo pálido.

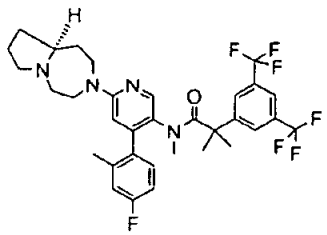
EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.95-7.89 (s, 1H); 7.80-7.69 (br.s, 2H); 7.74-7.64 (br.s, 1H); 7.19-7.11 (d, 1H); 6.71-6.65 (s, 1H); 4.77-4.64 (d, 1H); 4.45-4.32 (d, 1H); 3.72-3.59 (m, 1H); 3.52-3.41 (dd, 1H);

3.39-3.31 (m, 1H); 2.83-2.73 (t, 1H); 2.60-2.50 (m, 1H); 2.31-2.17 (s, 3H); 2.21-2.15 (m, 1H); 2.15-2.05 (s, 3H); 1.97-1.88 (m, 1H); 1.82-1.71 (m, 1H); 1.71-1.58 (m, 1H); 1.55-1.42 (s, 3H); 1.41-1.27 (s, 3H).

EJEMPLO 15

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*S*)-octahidro-3*H*-pirrolo[1,2-*d*][1,4]diazepin-3-il]-3-piridinil}-*N*,2-dimetilpropanamida (E15)



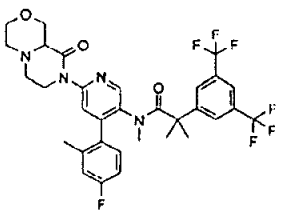
Un vial sellado de 8 ml se cargó con 60 mg (0.1 12 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 47 mg (0.335 mmoles) de (9a*S*)-octahidro-1*H*-pirrolo[1,2-*d*][1,4]diazepina (D6), 31 mg de carbonato de potasio (0.224 mmoles); los reactivos se disolvieron en 0.5 ml de DMSO. La mezcla de reacción se calentó a 150°C durante la noche y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 1:1, a 100% de acetato de etilo y dando 32 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): 8.02 (s, 1H), 7.93-7.82 (br.s, 1H), 7.79-7.70 (br.s, 2H), 7.73-7.64 (br.s, 1H), 7.15 (t, 1H), 7.13-7.03 (br. s, 1H), 6.66-6.52 (br. s, 1H), 4.28-3.98 (br. s, 1 H), 3.80-3.51 (br. s, 4H), 3.51-3.39 (br. s, 1H), 3.26-3.03 (br. s, 1H), 2.60-2.45 (br. s, 1H), 2.22 (s, 3H), 2.12 (s, 3H), 2.07-1.77 (br. s, 3H), 1.48 (s, 3H), 1.55-1.24 (m, 2H), 1.33 (s, 3H), 1.26-1.14 (m, 1H).

EJEMPLO 16

2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(9-oxohexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E16)



Un vial sellado de 8 ml se cargó con 150 mg (0.281 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 120 mg (0.768 mmoles) de hexahidropirazino[2,1-*c*][1,4]oxazin-9(6*H*)-ona (D7), 60 µl (0.563 mmoles) de N,N'-dimetiletilenodiamina, 110 mg (0.578 mmoles) de yoduro de cobre, 183 mg (0.562 mmoles) de carbonato de cesio; los reactivos se disolvieron en 4.5 ml de dioxano. La mezcla de reacción se agitó durante la noche a 150°C. El crudo se purificó por cromatografía (sílice, ciclohexano/EtOAc 90/10-30/70) dando el compuesto del título como un sólido blanco: 73 mg, 0.111 mmoles,

40% de rendimiento.

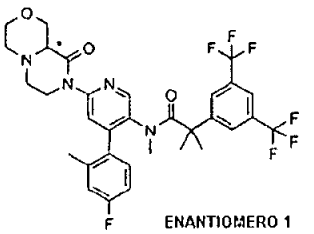
Rf: 0.55 (EtOAc)

EM (ES/+): 653 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.34-8.26 (s, 1H); 8.06-7.99 (s, 1H); 7.81-7.69 (br.s, 2H); 7.72-7.65 (br.s, 1H); 7.21-7.15 (d, 1H); 7.15-7.08 (s, 1H); 4.13-4.05 (dd, 1H); 4.03-3.82 (br.s, 2H); 3.80-3.72 (dd, 1H); 3.54-3.46 (dd, 1H); 3.40-3.31 (m, 1H); 3.14-3.06 (dd, 1H); 3.02-2.95 (dd, 1H); 2.86-2.80 (dd, 1H); 2.72-2.61 (m, 2H); 2.36-2.28 (t, 1H); 2.39-2.22 (br.s, 3H); 2.19-2.04 (br.s, 3H); 1.61-1.44 (br.s, 3H); 1.45-1.30 (br.s,3H).

EJEMPLO 17

2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(9-oxohexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E17) enantiómero 1 de E16



2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(9-oxohexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-N,2-dimetilpropanamida (E16; 42 mg) se sometió a separación quiral para aislar sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual se aisló usando las siguientes condiciones (20

mg, 100% e.e.)

Condiciones preparativas:

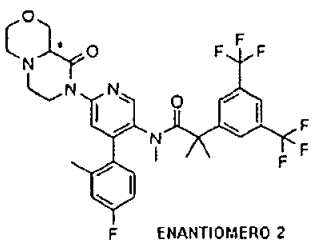
Cantidad suministrada	42 mg
Columna quiral	CHIRALCEL OD, (25 x 2) cm
Fase móvil	n-Hexano/2-propanol 94/6% v/v
Velocidad de flujo	18 ml/min
Detección	UV a 225 nm
Tiempo de corrida	17 min

EM (ES/+): 653 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.34-8.26 (s, 1H); 8.06-7.99 (s, 1H); 7.81-7.69 (br.s, 2H); 7.72-7.65 (br.s, 1H); 7.21-7.15 (d, 1H); 7.15-7.08 (s, 1H); 4.13-4.05 (dd, 1H); 4.03-3.82 (br.s, 2H); 3.80-3.72 (dd, 1H); 3.54-3.46 (dd, 1H); 3.40-3.31 (m, 1H); 3.14-3.06 (dd, 1H); 3.02-2.95 (dd, 1H); 2.86-2.80 (dd, 1H); 2.72-2.61 (m, 2H); 2.36-2.28 (t, 1H); 2.39-2.22 (br.s, 3H); 2.19-2.04 (br.s, 3H); 1.61-1.44 (br.s, 3H); 1.45-1.30 (br.s,3H).

EJEMPLO 18

2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(9-oxohexahidropirazino[2,1-c][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E18) enantiómero 2 de E16



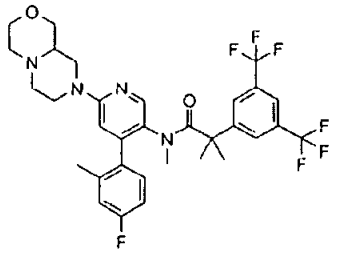
El compuesto del título se aisló usando las mismas condiciones como en E17, obteniendo 17 mg, 100% e.e.

EM (ES/+): 653 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.34-8.26 (s, 1H); 8.06-7.99 (s, 1H); 7.81-7.69 (br.s, 2H); 7.72-7.65 (br.s, 1H); 7.21-7.15 (d, 1H); 7.15-7.08 (s, 1H); 4.13-4.05 (dd, 1H); 4.03-3.82 (br.s, 2H); 3.80-3.72 (dd, 1H); 3.54-3.46 (dd, 1H); 3.40-3.31 (m, 1H); 3.14-3.06 (dd, 1H); 3.02-2.95 (dd, 1H); 2.86-2.80 (dd, 1H); 2.72-2.61 (m, 2H); 2.36-2.28 (t, 1H); 2.39-2.22 (br.s, 3H); 2.19-2.04 (br.s, 3H); 1.61-1.44 (br.s, 3H); 1.45-1.30 (br.s, 3H).

EJEMPLO 19

2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E19)



Un vial sellado de 8 ml se cargó con 124 mg (0.233 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577); 83 mg (0.584 mmoles) de octahidropirazino[2,1-*c*][1,4]oxazina (EP 472826), 90 mg (0.701 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.5 ml de DMSO. El

producto crudo se purificó por cromatografía instantánea (sílice, ciclohexano/EtOAc 90/10-30/70) dando el compuesto del título como un sólido blanco 85 mg (0.133 mmoles).

Rf: 0.4 (EtOAc)

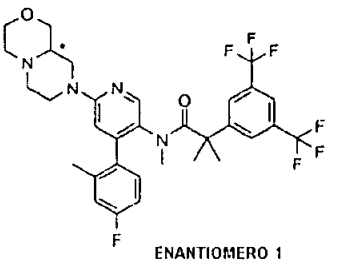
EM (ES/+): 639 $[M+H]^+$.

RMN (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.91-7.85 (s, 1H); 7.79-7.68 (m, 2H); 7.73-7.65 (br.s, 1H); 7.18-7.12 (d, 1H); 7.13-7.06 (br.s,1H); 6.73-6.64 (s, 1H); 4.29-4.18 (d, 1H); 4.13- 4.03 (d, 1H); 3.78-3.68 (t, 2H); 3.56-3.48 (t, 1H); 3.18-3.09 (t, 1H); 2.92-2.80 (t, 1H); 2.82-2.74 (d, 1H); 2.70-2.62 (d, 1H); 2.44-2.34 (t, 1H); 2.21-2.15 (s, 3H); 2.28-2.06 (m, 3H); 2.14-2.07 (s, 3H); 1.55-1.41 (s, 3H); 1.40-1.28 (s, 3H).

EJEMPLO 20

2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E20) enantiómero 1 de E19

[$[\alpha]_D$=1.8, c=1.0, MeOH]



ENANTIOMERO 1

El ejemplo 19 (15 mg) se sometió a separación quiral para aislar

sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual, se aisló usando las siguientes condiciones (5 mg, 97.2% e.e.) 440

Condiciones preparativas:

Cantidad suministrada	15 mg
Columna quiral	CHIRALCEL OD, (25 x 2) cm
Fase móvil	n-Hexano/2-propanol 94/6% v/v
Velocidad de flujo	18 ml/min
Detección	UV a 225 nm
Tiempo de corrida	17 min

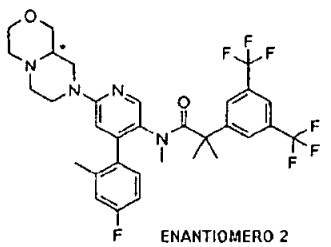
EM (ES/+): 639 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.91-7.85 (s, 1H); 7.79-7.68 (m, 2H); 7.73-7.65 0 (br.s, 1H); 7.18-7.12 (d, 1H); 7.13-7.06 (br.s,1H); 6.73-6.64 (s, 1H); 4.29-4.18 (d, 1H); 4.13-4.03 (d, 1H); 3.78-3.68 (t, 2H); 3.56-3.48 (t, 1H); 3.18-3.09 (t, 1H); 2.92-2.80 (t, 1H); 2.82- 2.74 (d, 1H); 2.70-2.62 (d, 1H); 2.44-2.34 (t, 1H); 2.21-2.15 (s, 3H); 2.28-2.06 (m, 3H); 2.14-2.07 (s, 3H); 1.55-1.41 (s, 3H); 1.40-1.28 (s, 3H).

EJEMPLO 21

2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E21) enantiómero 2 de E19

[[α]$_D$ =-1.0]



ENANTIOMERO 2

El compuesto del título se aisló usando las mismas condiciones como en E20, obteniendo 5 mg, 99.8% e.e.

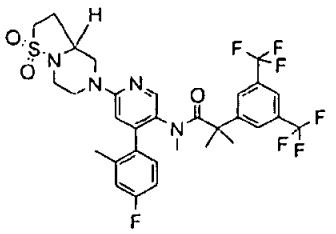
EM (ES/+): 639 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.05-7.98 (s, 1H); 7.91-7.85 (s, 1H); 7.79-7.68 (m, 2H); 7.73-7.65 (br.s, 1H); 7.18-7.12 (d, 1H); 7.13-7.06 (br.s,1H); 6.73-6.64 (s, 1H); 4.29-4.18 (d, 1H); 4.13-4.03 (d, 1H); 3.78-3.68 (t, 2H); 3.56-3.48 (t, 1H); 3.18-3.09 (t, 1H); 2.92-2.80 (t, 1H); 2.82-2.74 (d, 1H); 2.70-2.62 (d, 1H); 2.44-2.34 (t, 1H); 2.21-2.15 (s, 3H); 2.28-2.06 (m, 3H); 2.14-2.07 (s, 3H); 1.55-1.41 (s, 3H); 1.40-1.28 (s, 3H).

EJEMPLO 22

2-[3,5-Bis(trifluorometil)fenil]-*N*-[6-(1,1-dioxidohexahidro-5*H*-isotiazol[2,3-*a*]pirazin-5-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida

(E22) enantiómero 1 de E1



Condiciones preparativas:

Cantidad suministrada	37 mg
Columna quiral	CHIRALPAK AD-H, (25 x 2) cm
Fase móvil	n-Hexano/Etanol+ 0.1% de isopropilamina 25/75% v/v
Velocidad de flujo	15 ml/min
Detección	UV a 225 nm

Se aislaron: 4 mg; la pureza del enantiómero 1 resultó que era de 100%

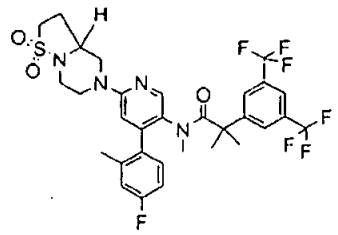
EM (ES/+): 673 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.08-6.85 (m, 3H); 6.53 (s, 1H); 4.81-4.53 (m, 1H); 4.35-4.09 (m, 1H); 3.53-3.50 (m, 1H); 3.38-3.25 (m, 1H); 3.16-3.09 (m, 1H); 2.96 (t, 1H); 2.83 (t, 1H); 2.70-1.98 (m, 10H); 1.79-1.47 (m, 3H); 1.46-1.33 (s, 3H).

EJEMPLO 23

2-[3,5-Bis(trifluorometil)fenil]-*N*-[6-(1,1-dioxidohexahidro-5*H*-isotiazol[2,3-*a*]pirazin-5-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida

(E23) enantiómero 2 de E1



Condiciones preparativas:

Columna quiral	CHIRALPAK AD-H, (25 x 2) cm
Fase móvil	n-Hexano/Etanol+ 0.1% de isopropilamina 25/75% v/v
Velocidad de flujo	15 ml/min
Detección	UV a 225 nm

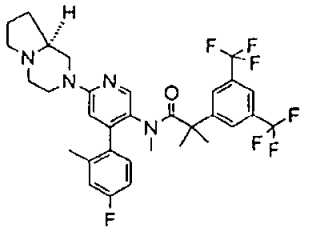
Se aislaron: 6 mg; la pureza del enantiómero 2 fue de 98.8% por UV

EM (ES/+): 673 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.08-6.85 (m, 3H); 6.53 (s, 1H); 4.81-4.53 (m, 1H); 4.35-4.09 (m, 1H); 3.53-3.50 (m, 1H); 3.38-3.25 (m, 1H); 3.16-3.09 (m, 1H); 2.96 (t, 1H); 2.83 (t, 1H); 2.70-1.98 (m, 10H); 1.79-1.47 (m, 3H); 1.46-1.33 (s, 3H).

EJEMPLO 24

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E24)



Un tubo de microondas de 10 ml se cargó con 80 mg (0.150 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 47.4 mg (0.375 mmoles) de (8a*S*)-octahidropirrolo[1,2-*a*]pirazina, 62.2 mg (0.450 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.6 ml de DMSO. La mezcla de reacción se irradió en un horno de microondas (180°C, 300W) durante 1 hora y después el crudo se purifica mediante un instrumento preparativo dirigido a la masa de Waters (System Fraction Lynx TM) relizada sobre una EM C18 X Terra Prep (30 x 150 mm; 10 µm) (fase móvil: de 99% [agua +0.1% de HCO2H] y 1% [CH_3CN +0.1% de HCO_2H] a 100% [CH_3CN +0.1% de HCO_2H] en 8 min y 30"; 100% [CH_3CN +0.1% de HCO_2H] durante 6 min; de 100% [CH_3CN +0.1% de HCO_2H] a 99% [agua +0.1% de HCO_2H] y 1% [CH_3CN +0.1% de HCO_2H] en 30"; 99% [agua +0.1% de HCO_2H] y 1% [CH_3CN +0.1% de HCO_2H] para 12"); T=t.a.; velocidad de flujo= 40 ml/min; Detección de UV :210-400 nm; Modo de detección de EM: ES (+)/ ES (-), Intervalo de masa:

100-900] para dar 45 mg del compuesto objetivo como sólido amarillo pálido.

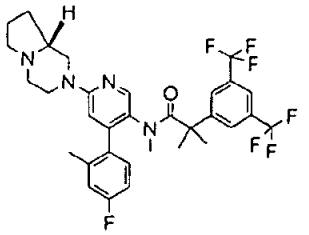
R_F = 0.2 (Acetato de etilo)

EM (ES/+): 623 $[M+H]^+$

RMN ($CDCl_3$): δ (ppm) 8.00 (s, 1H), 7.78 (s, 1H), 7.71-7.60 (br. s, 2H), 7.27-7.22 (br. s, 1H), 7.05-6.85 (br. s, 2H), 6.52-6.45 (s, 1H), 4.63-3.98 (m, 2H), 3.74-2.94 (m, 4H), 2.42-2.29 (s, 3H), 2.67-1.86 (m, 3H), 2.17-2.07 (s, 3H), 1.56-1.48 (s, 3H), 1.81-1.12 (m, 4H), 1.41-1.33 (s, 3H).

EJEMPLO 25

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E25)



El compuesto del título se preparó empezando a partir de 100 mg (0.187 mmole) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 70 mg (0.554 mmoles) de (8a*R*)-octahidropirrolo[1,2-*a*]pirazina, 52.2 mg de carbonato de potasio (0.377 mmoles); los reactivos se disolvieron en 0.6 ml de DMSO y la mezcla de reacción se calentó a 150°C durante la noche. Se obtuvieron, después de cromatografía instantánea, 52 mg del compuesto

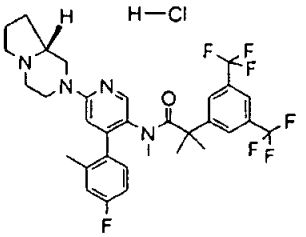
deseado.

EM (ES/+): 623 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.00 (s, 1H), 7.78 (s, 1H), 7.71-7.60 (br. s, 2H), 7.27-7.22 (br. s, 1H), 7.05-6.85 (br. s, 2H), 6.52-6.45 (s, 1H), 4.63-3.98 (m, 2H), 3.74-2.94 (m, 4H), 2.42-2.29 (S, 3H), 2.67-1.86 (m, 3H), 2.17-2.07 (s, 3H), 1.56-1.48 (s, 3H), 1.81-1.12 (m, 4H), 1.41-1.33 (s, 3H).

EJEMPLO 26

Clorhidrato de 2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E26)



2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8aR)-hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E25; 39 mg, 0.063 mmoles) se disolvió en DCM y la temperatura se bajó 0°C; HCl (solución 1M en Et_2O) 75 µl (0.075 mmoles) se añadió lentamente y, después, la mezcla de reacción se agitó a esta temperatura durante 30 min. Después, el solvente se removió y, el sólido obtenido se trituró con pentano.

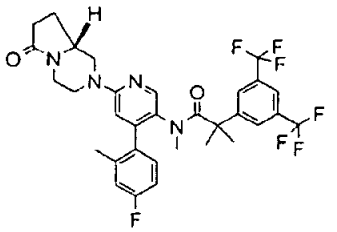
Se obtuvieron 41 mg del compuesto deseado como sólido amarillo pálido.

EM (ES/+): 623 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 10.63 (s, 1H), 8.02 (s, 1H), 7.96 (s, 1H), 7.81-7.65 (m, 2H), 7.17 (d, 1H), 7.15-7.07 (m, 1H), 6.90- 6.84 (s, 1H), 4.88-4.66 m, 1H), 4.12-1.08 (m, 24H).

EJEMPLO 27

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-6-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E27)



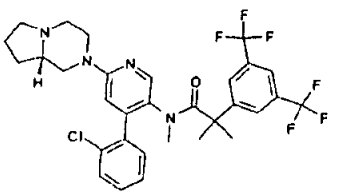
Un vial sellado de 8 ml se cargó con 100 mg (0.187 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 78.6 mg (0.561 mmoles) de (8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-6(2H)-ona (WO 2003/066635), 52 mg (0.374 mmoles) de carbonato de potasio; los reactivos se disolvieron en 0.8 ml de DMSO. La mezcla de reacción se calentó a 180°C durante 36-48 hr y después se añadió a una solución de NH_4Cl saturada y se extrajo nuevamente con DCM; el material crudo se purificó sobre cartucho de SPE (Sílice) eluyendo con un gradiente de ciclohexano/acetato de etilo 9:1, a 100% de acetato de etilo y dando 23 mg del compuesto deseado.

EM (ES/+): 637 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 8.01 (s, 1H); 7.78 (s, 1H); 7.65 (s, 2H); 7.05-6.87 (m, 3H); 6.52 (s, 1H); 4.67-4.52 (m, 1H); 4.32-4.19 (m, 1H); 4.14-4.10 (d, 1H); 3.77-3.64 (m, 1H); 3.02-2.84 (m, 2H); 2.61 (t, 1H); 2.48-2.44 (dd, 2H); 2.41-2.33 (s, 3H); 2.30-2.22 (m, 1H); 2.13 (s, 3H); 1.79-1.65 (m, 1H); 1.53 (s, 3H); 1.38 (s, 3H).

EJEMPLO 28

2-[3,5-Bis(trifluorometil)-fenil]-*N*-{4-(2-clorofenil)-6-[(8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E28)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-clorofenil)-3-piridinil]-N,2-dimetilpropanamida (WO 2005/002577; 0.11 mmoles) en DMSO seco (1 ml) *S*-octahidropirrolo[1,2-*a*]pirazina, (0.22 mmoles) y carbonato de potasio (0.22 mmoles) se añadieron y la mezcla resultante se agitó durante 12 horas a 150°C. Después de enfriarse, el diclorometano se añadió (2 ml) y después se añadió polímero de isocianato ligado (2.0 mmoles), y la mezcla resultante se agitó a temperatura ambiente durante la noche. Después la resina se filtró y el filtrado se concentró bajo

presión reducida. Las purificaciones se llevaron a cabo usando CLAR dirigida a la masa:

Condiciones cromatográficas preparativas

Columna:	X Terra EM C18 5 µm, 100 x 19 mm
Fase móvil:	A: sol. de NH_4HCO_3 10 mM, pH 10; B: CH_3CN
Gradiente:	30% (B) durante 1 min, de 30% (B) a 95% (B) en 9 min, 95% (B) durante 3 min
Velocidad de flujo:	20 ml/min
Intervalo de longitud de onda de UV:	210-350 nm
Intervalo de masa:	100-900 amu
Ionización:	ES+

Condiciones cromatográficas analíticas

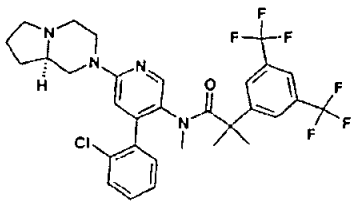
Columna:	X Terra EM C18 5 µm, 50 x 4.6 mm
Fase móvil:	A: Sol. de NH4HCO3 10 mM, pH10; B: CH_3CN
Gradiente:	30% (B) durante 1 min, de 30% (B) a 95% (B) en 9 min, 95% (B) durante 3 min
Velocidad de flujo:	1 ml/min
Intervalo de longitud de onda de UV:	210-350 nm
Intervalo de masa:	100-900 amu
Ionización:	ES+

Se obtuvieron 44.6 mg del compuesto deseado.

RMN ($CDCl_3$): δ (ppm) 8.03 (s, 1H), 7.90 (s, 1H), 7.74 (s, 2H), 7.54 (2, 2H), 7.49-7.39 (m, 2H), 7.27 (d, 1H), 6.72 (s, 1H), 4.39 (d, 1H), 4.22 (d, 1H), 3.05-2.98 (m, 2H), 2.90-2.83 (t, 1H), 2.57-2.46 (m, 1H), 2.42 (s, 3H), 2.12 (t, 1H), 2.04 (q, 1H), 1.97-1.61 (m, 4H), 1.45-1.19 (m, 7H).

EJEMPLO 29

2-[3,5-Bis(trifluorometil)-fenil]-*N*-{4-(2-clorofenil)-6-[(8a*R*)-hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E29)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-clorofenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577; 0.11 mmoles) en DMSO seco (1 ml) R-octahidropirrolo[1,2-*a*]pirazina, (0.22 mmoles) y carbonato de potasio (0.22 mmoles) se añadieron y la mezcla resultante se agitó durante 12 horas a 150°C. Después de enfriarse el diclorometano se añadió (2 ml) y después se añadió polímero de isocianato ligado (2.0 mmoles), y la mezcla resultante se agitó a temperatura ambiente durante la noche. Después la resina se filtró y el filtrado se concentró bajo presión reducida. Las purificaciones se llevaron a cabo usando CLAR dirigida a la masa:

Condiciones cromatográficas preparativas

Columna:	X Terra EM C18 5 µm, 100 x 19 mm
Fase móvil:	A: Sol. de NH_4HCO_3 10 mM, pH 10; B: CH_3CN
Gradiente:	30% (B) durante 1 min, de 30% (B) a 95% (B) en 9 min, 95% (B) durante 3 min
Velocidad de flujo:	20 ml/min

Intervalo de longitud de onda de UV:	210-350 nm
Intervalo de masa:	100-900 amu
Ionización:	ES+

Condiciones cromatográficas analíticas

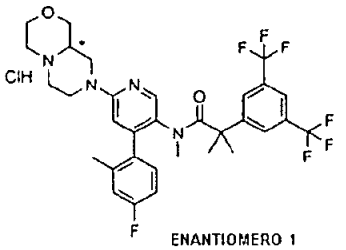
Columna:	X Terra EM C18 5 µm, 50 x 4.6 mm
Fase móvil:	A: Sol. de NH_4HCO_3 10 mM, pH10; B: CH_3CN
Gradiente:	30% (B) durante 1 min, de 30% (B) a 95% (B) en 9 min, 95% (B) durante 3 min
Velocidad de flujo:	1 ml/min
Intervalo de longitud de onda de UV:	210-350 nm
Intervalo de masa:	100-900 amu
Ionización:	ES+

Se obtuvieron 26.3 mg del compuesto deseado.

RMN (DMSO-d_6): δ (ppm) 8.03 (s, 1H), 7.90 (s, 1H), 7.74 (s, 2H), 7.54 (2, 2H), 7.49-7.39 (m, 2H), 7.27 (d, 1H), 6.72 (s, 1H), 4.39 (d, 1H), 4.22 (d, 1H), 3.05-2.98 (m, 2H), 2.90-2.83 (t, 1H), 2.57-2.46 (m, 1H), 2.42 (s, 3H), 2.12 (t, 1H), 2.04 (q, 1H), 1.97-1.61 (m, 4H), 1.45-1.19 (m, 7H).

EJEMPLO 30

Clorhidrato de 2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E30) enantiómero 1



ENANTIOMERO 1

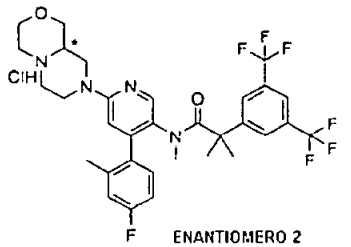
Una muestra de 2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E20, 42 mg, 66 µmoles) se suspendió en 1 ml de éter dietílico anhidro y se trató a 0°C durante 30 min con 79 µl de HCl 1M en éter dietílico. El solvente se removió bajo una corriente de nitrógeno y el producto se trituró con pentano anhidro, para dar, después de filtración, el clorhidrato como un sólido blanco (44 mg, cuantitativo).

EM (ES/+): 639 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 10.99 (br. s, 1H), 8.04 (s, 1H), 7.95 9s, 1H), 7.85-7.60 (m, 2H), 7.19 (d, 1H), 7.16-6.92 (m, 2H), 6.92-6.80 (s, 1H), 4.56 (d, 1H), 4.43 (d, 1H), 4.12-3.93 (m, 2H), 3.81 (t, 1H), 3.59 (t, 1H), 3.52-3.45 (m, 1H), 3.29-3.12 (m, 3H), 3.05-2.79 (m, 1H), 2.60-2.52 (m, 1H), 2.33-2.20 (br. s, 3H), 2.22-2.14 (m, 1H), 2.16-2.05 (br. s, 3H), 1.56-1.09 (m, 6H).

EJEMPLO 31

Clorhidrato de 2-[3,5-Bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E31) enantiómero 2



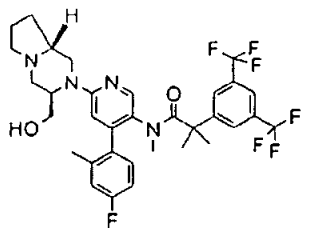
Una muestra de 2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-3-piridinil]-*N*,2-dimetilpropanamida (E21; 39 mg ,61 µmoles) se suspendió en 1 ml de éter dietílico anhidro y se trató a 0°C durante 30 min con 73 µl de HCl 1M en éter dietílico. El solvente se removió bajo una corriente de nitrógeno y el producto se trituró con pentano anhidro, para dar, después de filtración, el clorhidrato como un sólido blanco 41 mg.

EM (ES/+): 639 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 10.99 (br. s, 1H), 8.04 (s, 1H), 7.95 9s, 1H), 7.85-7.60 (m, 2H), 7.19 (d, 1H), 7.16-6.92 (m, 2H), 6.92-6.80 (s, 1H), 4.56 (d, 1H), 4.43 (d, 1H), 4.12-3.93 (m, 2H), 3.81 (t, 1H), 3.59 (t, 1H), 3.52-3.45 (m, 1H), 3.29-3.12 (m, 3H), 3.05-2.79 (m, 1H), 2.60-2.52 (m, 1H), 2.33-2.20 (br. s, 3H), 2.22-2.14 (m, 1H), 2.16-2.05 (br. s, 3H), 1.56-1.09 (m, 6H).

EJEMPLO 32

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*R*,8a*R*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E32)



El compuesto del título se preparó empezando a partir de 323 mg (0.608 mmoles) de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577), 1.216 mg (0.160 mmoles) de (3*R*,9a*R*)-octahidro-2*H*-pirido[1,2-*a*]pirazin-3-ilmetanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005), 35 mg de bis(dibencilidenoacetona)paladio (0.061 mmoles), 57 mg de 2-diciclohexilfosfino-2'-(*N*,*N*-dimetilamino)bifenilo (0.145 mmoles), 297 mg (0.912 mmoles) de carbonato de cesio; los reactivos se disolvieron en 10 ml de tolueno y se agitaron a 140°C en un vial cerrado durante 4 horas. Más diciclohexilfosfino-2'-(*N*,*N*-dimetilamino)bifenilo (57 mg 0.145 mmoles), y bis(dibencilidenoacetona)paladio (35 mg, 0.061 mmoles) se añadieron y la reacción se mantuvo a 140°C durante 4 horas adicionales. El material crudo se cargó sobre un cartucho de SCX, las fracciones neutras se lavaron con metanol y la básica se eluyó con amoniaco 2M en metanol y se recogió. El solvente se removió y el residuo se purificó por cromatografía (Sílice)

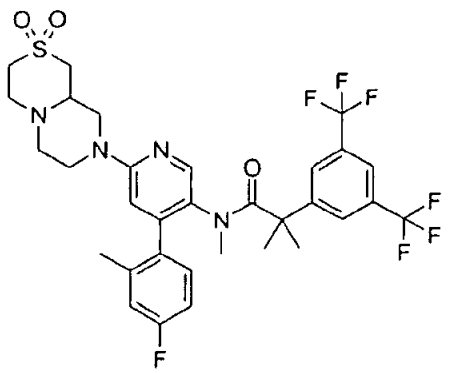
eluyendo con acetato de etilo, seguido por un dradiente de cloruro de metileno a cloruro de metileno:metanol 95:5. Las fracciones más limpias se purificaron adicionalmente por cromatografía sobre un cartucho de NH_2-sílice con un gradiente de ciclohexano a ciclohexano:acetato de etilo 70:30, dando 29 mg del compuesto del título como sólido amarillo pálido.

EM (ES/+): 653 $[M+H]^+$

RMN (DMSO-d_6): δ (ppm) 7.89-7.86 (s, 1H); 7.80-7.76 (s, 1H); 7.70-7.66 (s, 2H); 7.12-7.03 (m, 2H); 7.00-6.92 (m, 1H); 6.50-6.47 (s,1H); 4.06-3.97 (m, 1H); 3.66-3.54 (m, 3H); 3.49-3.39 (m, 1H); 3.27-3.12 (m, 1H); 3.11-3.00 (m, 1H); 2.89-2.77 (m, 2H); 2.44-2.38 (s, 3H); 2.17-2.07 (s, 3H); 2.07-1.41 (m, 5H); 1.38-1.31 (s, 3H); 1.26-1.20 (s, 3H).

EJEMPLO 33

2-[3,5-Bis(trifluorometil)fenil]-*N*-[6-(2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E33)



Un vial sellado de 8 ml se cargó con 180 mg (0.31 mmoles) de 2-

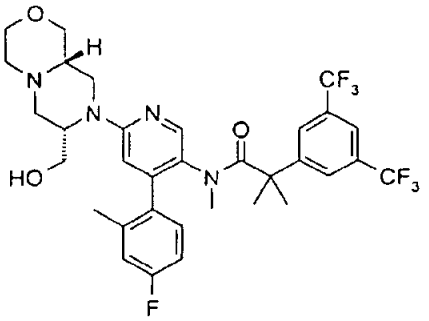
[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (WO 2005/002577); 168 mg (0.62 mmoles) de 2,2-dióxido de octahidropirazino[2,1-*c*][1,4]tiazina (D19), 128 mg (0.701 mmoles) de carbonato de potasio; los reactivos se disolvieron en 1 ml de DMSO y se agitaron a 150°C durante 18 hr. La mezcla de reacción se diluyó con agua y acetato de etilo y la fase acuosa se extrajo con acetato de etilo. Las fracciones orgánicas combinadas se secaron y el solvente se removió bajo presión reducida. El producto crudo se purificó por cromatografía instantánea (sílice, ciclohexano/EtOAc 50/50 a EtOAc) dando el compuesto del título como un sólido blanco 105 mg.

EM (ES/+): $[M+Na]^+$

RMN (DMSO-d_6): δ (ppm) 8.07-7.99 (s, 1H), 7.97-7.86 (s, 1H), 7.82-7.62 (m, 2H), 7.22-7.12 (d, 1H), 7.15-6.98 (m, 2H), 6.79-6.69 (s, 1H), 4.32-4.13 (m, 2H), 3.31-3.07 (m, 5H), 3.04-2.84 (m, 3H), 2.73-2.55 (m, 2H), 2.57-2.43 (m, 3H), 2.36-2.18 (m, 1H), 2.29-2.05 (m, 3H); 1.60-1.27 (m, 6H).

EJEMPLO 34

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E34)



2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D24) (390 mg, 0.498 mmoles) se disolvió 17 ml de metanol. A esta solución se añadió HCl concentrado (0.9 ml) a 0°C, y la agitación se continuó a temperatura ambiente durante 3 hr (conversión completa). La mezcla de reacción se cargó sobre un cartucho de SCX y se lavó con MeOH. El producto se eluyó con amoniaco metanólico 0.5 M. Las fracciones que contenían producto se evaporaron, dejando el compuesto objetivo como un sólido blanco: 310 mg, 0.464 mmoles, 93%.

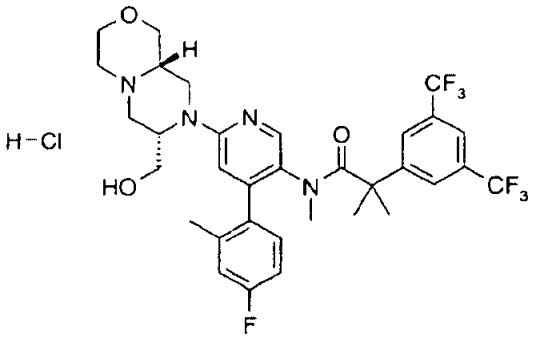
UPLC/MS: m/z= 669 (M+1).

^{1}H-RMN (DMSO-d_6): δ (ppm) 8.07-7.97 (s, 1H), 7.88-7.81 (s, 1H), 7.79-7.69 (br. s, 2H), 7.19-7.11 (d, 1H), 7.14-7.06 (br. s, 2H) 6.64-6.56 (s, 1H), 4.75-4.65 (m, 1H), 4.31-4.13 (br. s, 1H), 4.15-4.01 (br. s, 1H), 3.80-3.68 (m, 3H), 3.58-3.49 (t, 1H); 3.43-3.34 (m, 1H); 3.18-3.09 (t, 1H); 3.04-2.98 (d, 1H);

2.68-2.58 (d, 1H); 2.51-2.45 (s, 3H); 2.20-2.13 (s, 3H); 2.29-2.00 (m, 4H); 1.54-1.39 (s, 3H); 1.39-1.28 (s, 3H).

EJEMPLO 35

Clorhidrato de 2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E35)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E34) (300 mg, 0.449 mmoles) en 2 ml de éter dietílico se añadieron 0.6 ml de una solución HCl 1M en éter dietílico. Se formó un precipitado blanco. El solvente y exceso de HCl se removieron bajo una corriente de nitrógeno y el residuo se trituró con 1 ml de 1:1 de pentano:Et_2O. El sólido blanco se recogió por filtración y se dejó bajo alto vacío para dar el compuesto del título 280 mg, 0.397 mmoles, 88% de rendimiento.

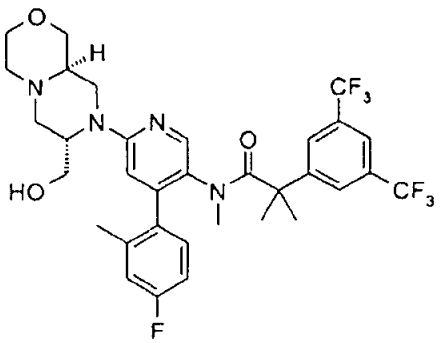
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 10.24 (br. s., 1H) 8.03 (br.

s., 1H) 7.90 (br. s., 1H) 7.55-7.82 (m, 2H) 6.89-7.24 (m, 3 H) 6.77 (br. s., 1H) 4.65 (br. s., 1H) 4.45 (br. s., 1H) 3.92-4.15 (m, 2H) 3.76-3.90 (m, 2H) 3.34-3.55 (m, 2H) 3.09-3.36 (m, 2H) 2.84-3.04 (m, 1H) 2.49-2.62 (m, 2H) 2.01-2.30 (m, 6 H) 1.10-1.58 (m, 8 H).

α_D (c = 0.5 en MeOH) = -39.6 obtenido usando un polarímetro polAAR 3000, λ = 589.4 nm, volumen de celda = 1.3 ml, longitud de trayectoria, l = 1dm. (Este valor se determinó en una muestra diferente, espectroscópicamente la misma que se describió antes y preparada de una manera análoga).

EJEMPLO 36

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*S*,9a*R*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E36)



2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-N,2-dimetilpropanamida (D25) (87 mg, 0.111 mmoles) se

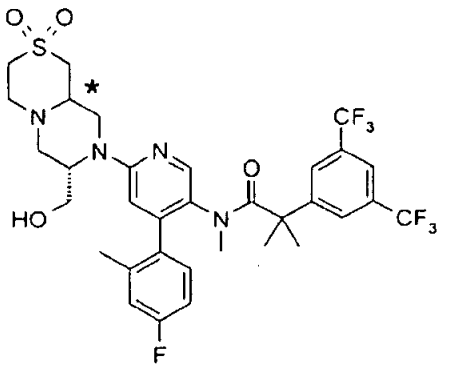
disolvió 4 ml de metanol. A esta solución se añadió HCl concentrado (0.2 ml) a 0°C, y se agitó a temperatura ambiente durante 1 hr (conversión completa). La mezcla de reacción se cargó sobre un cartucho de SCX y se lavó con MeOH. El producto se eluyó con amoniaco metanólico 0.5 M. Las fracciones básicas UV-activas se evaporaron, dejando el compuesto objetivo como un sólido blanco: 69 mg, 0.103 mmoles, 93%.

EM: m/z= 669 (M+1).

^{1}H-RMN (DMSO-d_6): δ (ppm) 8.07-7.97 (m, 1H), 7.95-7.89 (br. s, 1H), 7.81-7.67 (br. s, 2H), 7.20-7.10 (d, 1H), 7.16-7.04 (br. s, 2H), 6.75-6.65 (br. s, 1H), 4.87-4.78 (br. s, 1H), 3.96- 3.79 (br. s, 1H), 3.66-3.47 (m, 4H), 3.42-3.34 (m, 1H), 3.32-3.23 (m, 1H); 3.17-3.07 (dd, 1H); 2.71-2.63 (dd, 1H); 2.61-2.39 (m, 2H); 2.50-2.44 (s, 3H); 2.39-1.99 (m, 3H); 2.16-2.02 (br. s, 3H); 1.58-1.42 (s, 3H); 1.40-1.27 (s, 3H).

EJEMPLO 37

2-[3,5-Bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*S*, 9a*R* o 9a*S*)-7-(hidroximetil)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E37)-Diaestereoisómero 1



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*, 9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)(dirnetil)silil]oxi}metil)-2,2-dioxidohexahidropirazino [2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D31) (170 mg, 0.2 mmoles) en 8 ml de metanol se añadió gota a gota HCl 12N (0.4 ml) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 1.5 hr, después se purificó por cartucho de SCX para dar el compuesto del título como un sólido blanco (120 mg, rendimiento = 81 %).

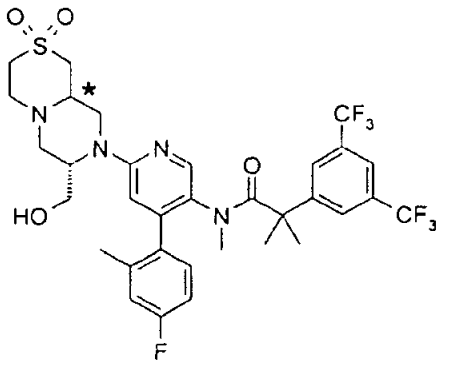
CLAR : pico a t=5.54 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.85 (s, 1H) 7.63-7.81 (m, 2H) 7.16 (d, 1H) 7.03-7.17 (m, 2H) 6.67 (s, 1H) 4.71 (t, 1H) 4.19-4.36 (m, 1H) 4.02-4.19 (m, 1H) 3.65-3.80 (m, 1H) 3.36-3.53 (m, 1H) 3.24-3.36 (m, 2H) 3.15-3.29 (m, 2H) 3.10 (d, 1H) 2.86-3.01 (m, 1H) 2.72-2.84 (m, 1H)

2.65 (d, 1H) 2.49 (s, 3 H) 2.42-2.56 (m, 2H) 2.20 (s, 3 H) 1.49 (s, 3 H) 1.34 (s, 3 H).

EJEMPLO 38

2-[3,5-Bis(trifluorometil)fenil]-N-{4-(4-fluoro-2-metilfenil)-6-[(7*S*, 9a*S* o *R*)-7-(hidroximetil)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida (E38)-Diaestereómero 2



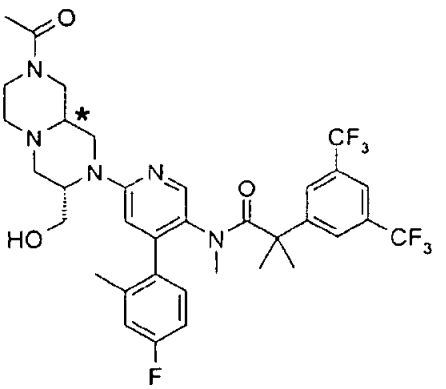
2-[3,5-Bis(trifluorometil)fenil]-N-[6-[(7*S*, 9a*S* o *R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2,2-dioxidohexahidropirazino[2,1-c][1,4]tiazin-8(1H)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-N,2-dimetilpropanamida (D36) (158 mg, 0.190 mmoles) se disolvió 10 ml de metanol. A esta solución se añadió gota a gota HCl concentrado (0.4 ml) a 0°C, y se agitó a temperatura ambiente durante 1.5 hr (conversión completa por UPLC/MS, pico a 0.87 min., m/z = 717 (M+1), 359 ($^{M}/_{2}$ +1). La mezcla de reacción se purificó por cartucho de SCX, dejando el compuesto objetivo como un sólido: 107 mg, 0.149 mmoles, 78%.

EM: m/z= 669 (M+1).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.97-8.07 (m, 1H) 7.81-7.93 (m, 1H) 7.62-7.81 (m, 2H) 6.90-7.24 (m, 3 H) 6.57-6.71 (m, 1H) 4.65-4.76 (m, 1H) 4.09-4.38 (m, 1H) 3.65-3.79 (m, 1H) 3.30-3.49 (m, 2H) 3.05-3.28 (m, 5 H) 3.00 (t, 1H) 2.65-2.79 (m, 1H) 2.37-2.50 (m, 1H) 2.01-2.33 (m, 7 H) 1.10-1.55 (m, 6 H).

EJEMPLO 39

N-[6-[(3*S*, 9a*R* o *S*)-8-acetil-3-(hidroximetil)octahidro-2*H*-pirazino[1,2-*a*] pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil) fenil]-*N*,2-dimetilpropanamida (E39)-Diaestereoisómero 1



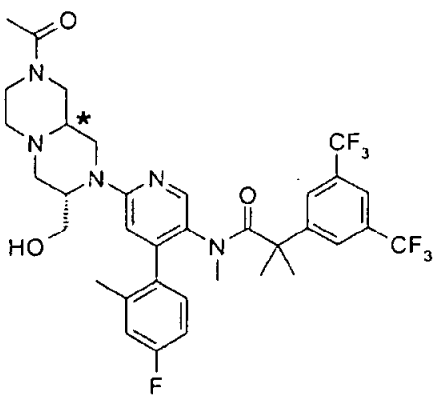
N-[6-[(3*S*, 9a*R* o *S*)-8-acetil-3-({[(1,1-dimetiletil)(dimetil)silil] oxi}metil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (D41) (1.168 g, 1.42 mmoles) se disolvió en 40 ml de metanol. A esta solución se añadió HCl concentrado (2.5 ml) a 0°C, y se agitó a temperatura ambiente durante 1 hr. El análisis de UPLC/MS mostró la conversión completa al producto esperado (pico a 0.75 min, m/z = 710 (M+1), 355.7 ($^M/_2$ +1)). La mezcla de reacción se

purificó por cartucho de SCX, seguido por cromatografía instantánea (CH_2Cl_2 → CH_2Cl_2: MeOH 92.5:7.5), para dar compuesto objetivo como un sólido: 483 mg,- mmoles, 78%.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.97-8.06 (m, 1H) 7.80-7.89 (m, 1H) 7.60-7.80 (m, 2H) 6.90-7.24 (m, 3 H) 6.54-6.76 (m, 1H) 4.66-4.74 (m, 1H) 4.04-4.43 (m, 2H) 3.67-3.91 (m, 2H) 3.32-3.47 (m, 1H) 3.13-3.23 (m, 1H) 3.00-3.10 (m, 1H) 2.68-2.87 (m, 2H) 2.55-2.69 (m, 2H) 1.78-2.40 (m, 12H) 1.11-1.58 (m, 6 H)

EJEMPLO 40

N-[6-[(3*S*, 9a*S* o *R*)-8-acetil-3-hidroximetil)octahidro-2*H*-pirazino[1,2-*a*] pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil) fenil]-*N*,2-dimetilpropanamida (E40)-Diaestereoisómero 2



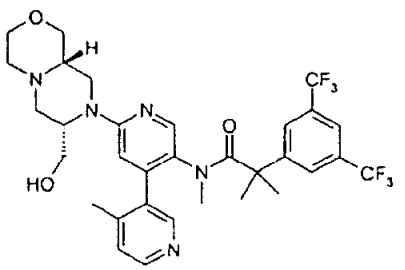
N-[6-[(3*S*, 9a*S* o *R*)-8-acetil-3-({[(1,1-dimetiletil)(dimetil)silil]oxi} metil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (D42) se trató como se describió para *N*-[6-[(3*S*, 9a*R* o *S*)-8-acetil-3-({[(1,1-dimetiletil)

(dimetil)silil]oxi}metil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (D41) anterior. El análisis de UPLC/MS mostró la conversión completa al producto esperado (pico a 0.71 min, m/z = 710 (M+1), 355.7 ($^{M}/_{2}$ +1)). El producto se purificó de la misma manera, dando 700 mg.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.97-8.06 (m, 1H) 7.86-7.94 (m, 1H) 7.61-7.82 (m, 2H) 6.92-7.21 (m, 3 H) 6.64-6.79 (m, 1H) 4.75-4.84 (m, 1H) 4.05-4.17 (m, 1H) 3.90-4.05 (m, 1H) 3.45-3.69 (m, 4 H) 3.33-3.45 (m, 1H) 3.18-3.30 (m, 1H) 3.05-3.18 (m, 2H) 2.69-2.83 (m, 1H) 2.51-2.64 (m, 2H) 2.32-2.45 (m, 2H) 2.05-2.29 (m, 5 H) 1.93-2.01 (m, 3 H) 1.09-1.56 (m, 6 H).

EJEMPLO 41

2-[3,5-bis(trifluorometil)fenil]-*N*-{6'-[(7*S*,9a*S*)-7-(hidroximetil) hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-metil-3,4'-bipiridin-3'-il}-*N*,2-dimetilpropanamida (E41)



2-[3,5-bis(trifluorometil)fenil]-*N*-{6'-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil) (dimetil)silil]oxi}metil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-metil-3,4'-bipiridin-3'-il}-*N*,2-dimetilpropanamida (D53, 86 mg) se disolvió en MeOH seco

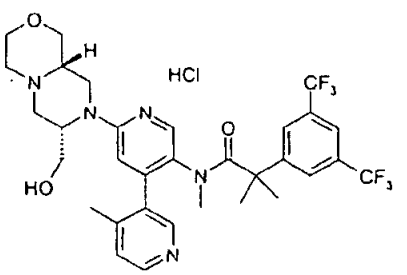
(4 ml), se enfrió en un baño de hielo/sal a ~0°C antes de añadir solución de HCl concentrada. La mezcla se agitó a ~0°C durante 45 min antes de dejar que se calentara hasta T.A. y agitando durante 2 hr adicionales. Se colocó sobre una columna de SCX 5g, se lavó con MeOH x3, antes de eluir el compuesto con NH_3 en MeOH. El solvente se evaporó. El residuo se purificó sobre a columna sek pak 5g eluyendo con Pent a EtOAc a 10% de MeOH/EtOAc. El solvente se evaporó a sequedad bajo vacío para dar una goma incolora del compuesto del título.

RMN (DMSO-d6) δ 8.44 (1 H, d), 8.21 (1 H, s), 8.04 (1 H, s), 7.89 (1 H, s), 7.73 (2H, s), 7.33 (1 H, d), 6.70 (1 H, s), 4.71 (1 H, br t), 4.23 (1 H, br s), 4.10 (1 h, br s), 3.76 (3H,m), 3.55 (1 H, t), 3.41 (2H, m), 3.16 (1 H, t), 3.02 (1 H, d), 2.66 (1 H, m), 2.33-2.05 (7H, m), 1.47-1.17 (6H, br m)

EM (API+): m/z 652.1 (MH+; 20%).

EJEMPLO 42

Clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{6'-[(7*S*,9a*S*)-7-(hidroximetil) hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-metil-3,4'-bipiridin-3'-il}-*N*,2-dimetilpropanamida (E42)

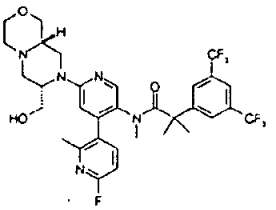


El compuesto del título se hizo disolviendo 2-[3,5-bis(trifluorometil)fenil]-*N*-{6'-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-metil-3,4'-bipiridin-3'-il}-*N*,2-dimetilpropanamida (E41, 33.8 mg) en un mínimo de DCM, añadiendo solución de HCl 1M en Et_2O, añadiendo Et_2O, triturando hasta que se precipita un sólido. Las soluciones madre se removieron. Se añadió más Et_2O para triturar nuevamente. El solvente se secó por soplado para dar un sólido blanco.

EM (API+): m/z = 652.3 (MH+; 20%)

EJEMPLO 43

2-[3,5-bis(trifluorometil)fenil]-*N*-{6-fluoro-6'-[(7*S*,9a*S*)-7-(hidroximetil) hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-2-metil-3,4'-bipiridin-3'-il}-*N*,2-dimetilpropanamida (E43)



2-[3,5-bis(trifluorometil)fenil]-*N*-(6'-cloro-6-fluoro-2-metil-3,4'-bipiridin-3'-il)-*N*,2-dimetilpropanamida (D54, 53.5 mg, 0.1 mmoles), (7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (051, 37 mg, 0.13 mmoles) se disolvieron en tolueno (1.5 ml). Bis tri-ter-butilfosfinpaladio (13 mg, 0.026 mmoles), seguido por cloruro de hexadeciltrimetilamonio (10 µl, solución acuosa al 25%), y finalmente solución

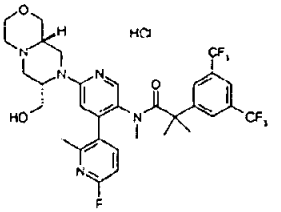
de hidróxido de sodio (0.13 ml, solución acuosa al 50%). La mezcla se desgasificó durante 5 minutos antes de calentarse a 90°C durante 4.5 horas. Se enfrió a T.A., se diluyó con EtOAc, se lavó con solución de $NaHCO_3$ saturada, se secó ($MgSO_4$). Se filtró. El solvente se evaporó. El residuo se purificó por columna de SCX, lavando con MeOH antes de eluir con NH_3 en MeOH. El solvente se evaporó. El residuo se purificó por cromatografía en columna eluyendo con Pent a EtOAc a 10% de MeOH/EtOAc. El solvente se evaporó bajo presión reducida para dar un sólido incoloro del compuesto del título (11 mg).

RMN (400MHz, CDCl3) δ 7.98 (1 H, s), 7.79 (1H, s), 7.73-7.70 (1H, br m), 7.64 (1H, s), 6.82 (1H, s), 6.43 (1H, s), 4.55 (1H, d), 4.02 (2H, s), 3.90 (1H, d), 3.81 (2H, t), 3.67 (1H, m), 3.33 (1H, 1), 3.12-3.06 (2H, m), 2.77 (1H, d), 2.54-2.30 (10H, m), 1.49 (3H, s), 1.35 (3H, s)

EM (API+): m/z 670.3 (MH+; 100%)

EJEMPLO 44

Clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{6-fluoro-6'-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-2-metil-3,4'-bipiridin-3'-il}-*N*,2-dimetilpropanamida (E44)

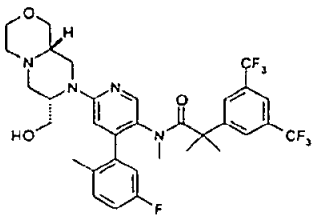


Sal de HCl se hizo como se describió en el ejemplo 41 empezando a partir de 2-[3,5-bis(trifluorometil)fenil]-*N*-{6-fluoro-6'-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-2-metil-3,4'-bipiridin-3'-il}-*N*,2-dimetilpropanamida (E43, 11.3 mg)para dar un sólido blanquecino.

EM (API+): m/z 670.3 (MH+; 100%)

EJEMPLO 45

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(5-fluoro-2-metilfenil)-6-[(7*S*,9a*S*)-7-hidroximetil)hexahidropirazino[2,1-*c*] [1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E45)



2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(5-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D56, 110 mg) se disolvió en MeOH seco (2 ml), se enfrió en un baño de hielo con sal antes de añadir solución de HCl (~0.2 ml), y agitando a T.A. durante 2 horas. Se vació directamente en una columna de SCX 5g. Se lavó con MeOH (2 x10 ml), antes de eluir el compuesto con NH_3 en MeOH 94 x10 ml). El solvente se evaporó. El residuo se purificó sobre una columna sek-pak 5g eluyendo con Pent a EtOAc a 10% de MeOH/EtOAc. El solvente se evaporó para dar el

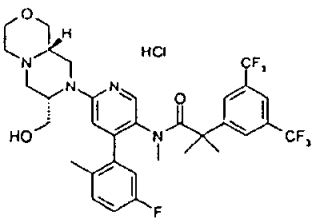
compuesto del título como un sólido blanco.

RMN (400MHz; CDCl3) δ 7.98 (1H, br s), 7.77 (1H, s), 7.67 (2H, s), 7.21 (1H, br s), 7.00 (2H, m), 6.44 (1H, s), 4.57 (1H, br s), 4.20-4.08 (1H, br m), 4.02 (2H, s), 3.89 (1H, dd), 3.81 (2H, d), 3.70 (1H, m), 3.33 (1H, 1), 3.11-3.05 (2H, m), 2.76 (1H, d), 3.63 (1H, d), 2.42-2.30 (4H, m), 2.29-2.05 (4H, m), 1.51-1.32 (6H, m)

EM (API+): m/z 669.3 (MH+; 100%)

EJEMPLO 46

Clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(5-fluoro-2-metilfenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E46)

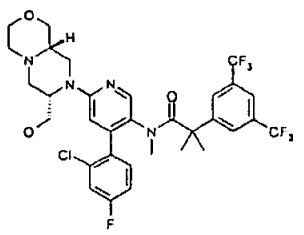


Sal de HCl se hizo de conformidad con el método descrito en el ejemplo 41 empezando a partir de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(5-fluoro-2-metilfenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E45, 11.5 mg) para dar un sólido amarillo pálido.

EM (API+): m/z 669.3 (MH+; 100%)

EJEMPLO 47

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(2-cloro-4-fluorofenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E47)



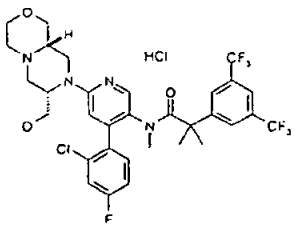
2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(2-cloro-4-fluorofenil)-6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (D58, 22 mg, 0.027 mmoles) se disolvió en MeOH seco (2 ml), se enfrió en un baño de hielo con sal a ~0°C antes de añadir solución de HCl concentrada (~ 0.1 ml), lentamente. La mezcla de reacción se agitó a ~0°C durante 1 hora antes de calentarse y agitarse a T.A. durante 2 horas. Se colocó directamente en una columna de SCX 2g, lavando con MeOH (2 x 5 ml) antes de eluir el compuesto con NH_3 en MeOH (4 x 5 ml). El solvente se evaporó bajo presión reducida para dar el compuesto del título como un sólido blanquecino (10 mg).

RMN (400MHz, DMSO-d6) δ 8.03 (1 H,s), 7.89 (1 H, s), 7.71 (2H, s), 7.55 (1 H, d), 7.34 (2H, m), 6.65 (1 H, s), 4.71 (1 H, t), 4.22 (1H, br m), 4.07 (1 H, br m), 3.76 (2H, m), 3.55 (1 H, t), 3.15 (1 H, t), 3.03 (1 H, m), 2.68-2.60 (2H, m), 2.50-2.40 (3H, m), 2.18-2.05 (3H, m), 1.45 (3H, s), 1.31 (3H, s)

EM (API+): m/z 689.3 (MH+; 100%)

EJEMPLO 48

Clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(2-cloro-4-fluorofenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E48)

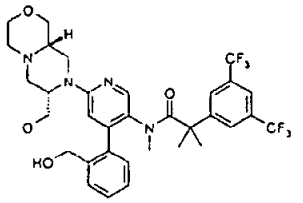


Sal de HCl se hizo de conformidad con el método descrito en el ejemplo 41 empezando a partir de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(2-cloro-4-fluorofenil)-6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E47, 10 mg) para dar un sólido amarillo pálido.

EM (API+): m/z 689.2 (MH+; 100%)

EJEMPLO 49

2-[3,5-bis(trifluorometil)fenil]-*N*-{6-[(7*S*,9a*S*)-7-(hidroximetil) hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-[2-(hidroximetil)fenil]-3-piridinil}-*N*,2-dimetilpropanamida (E49)



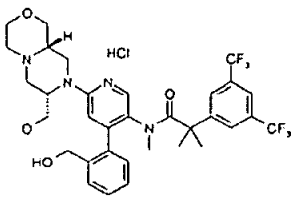
2-[3,5-bis(trifluorometil)fenil]-*N*-{6-[(7*S*,9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-[2-(hidroximetil)fenil]-3-piridinil}-*N*,2-dimetilpropanamida (D61, 24.6 mg, 0.0315 mmoles) se suspendió en MeOH seco (1 ml) antes de añadir solución de HCl concentrada (5 gotas). La mezcla de reacción después se agitó a T.A. durante 3 horas. Se vació directamente en una columna de SCX 5g, lavando con MeOH (2 x 10 ml) antes de eluir el compuesto con NH_3 en MeOH (4 x 10 ml). El solvente se evaporó. El residuo se purificó sobre una columna sek pak 5g eluyendo con 0-100% de EtOAc/Pent seguido por 0-10% de MeOH/EtOAc. El solvente se evaporó para dar el compuesto del título como una goma incolora.

RMN (400MHz, CDCl3) δ 7.94 (1 H, d), 7.78 (1 H, s), 7.66-7.59 (3H, m), 7.43 (1 H, t), 7.28 (1 H, m), 7.00-6.96 (1 H, m), 6.46 (1 H, d), 4.67 (1H, m), 4.53 (1H, d), 4.42-4.34 (1 H, m), 4.05-3.98 (2H, m), 3.90-3.67 (6H, m), 3.35-3.30 (1 H, m), 3.09-3.00 (2H, m), 2.72 (3H, d), 2.63 (1 H, dd), 2.45-2.30 (3H, m), 1.30 (6H, s)

EM (API+): m/z 667.3 (MH+; 100%)

EJEMPLO 50

Clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{6-[(7*S*,9a*S*)-7-(hidroximetil) hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-[2-(hidroximetil)fenil]-3-piridinil}-*N*,2-dimetilpropanamida (E50)

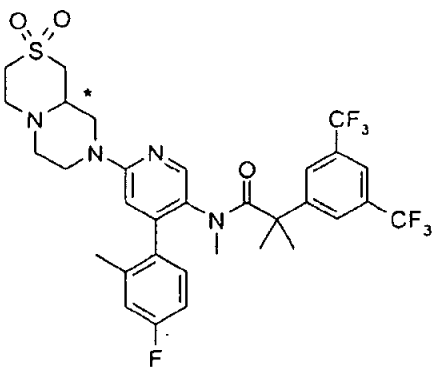


Sal de HCl se hizo de conformidad con el método descrito en el ejemplo 41 empezando a partir de 2-[3,5-bis(trifluorometil)fenil]-*N*-{6-[(7*S*,9a*S*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-[2-(hidroximetil)fenil]-3-piridinil}-*N*,2-dimetilpropanamida (E49, 10.2 mg) para dar un sólido amarillo.

EM (API+): 667.3 (MH+; 100%)

EJEMPLO 51

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(9a*R* o 9a*S*)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E51- Enantiómero 1)



N-[6-(8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E33, 101 mg) se sometió a separación quiral para aislar sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual se aisló usando condiciones preparativas descritas a continuación (se obtuvieron 12 mg de compuesto del título, >95%e.e., tiempo de retención analítico 10.23 min).

Condiciones de SFC semipreparativa (Gilson):

Cantidad suministrada	101 mg
Columna quiral	CHIRALCEL OD-H, (25 x 2) cm
Fase móvil	n-Hexano/2-propanol 94/6% v/v
Velocidad de flujo	18 ml/min
Detección	UV a 225 nm

Condiciones de SFC analítica (Berger):

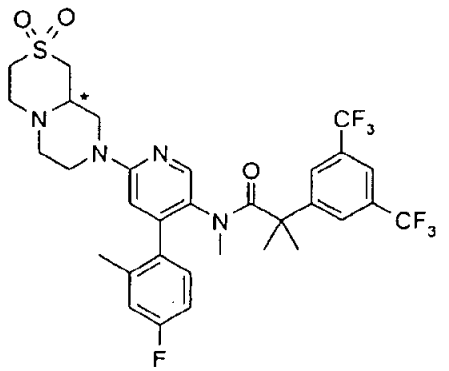
Columna quiral	CHIRALCEL OD, (25 x 2) cm
Fase móvil	n-Hexano/etanol 70/30% v/v
Velocidad de flujo	0.8 ml/min
Detección	UV a 225 nm

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (br. s., 1H) 7.89 (br. s., 1H) 7.61-7.84 (m, 2H) 7.16 (d, 1H) 6.90-7.14 (m, 2H) 6.72 (br. s., 1H) 4.12-4.31 (m, 2H) 3.08-3.32 (m, 5 H) 2.85-3.03 (m, 3 H) 2.52-2.73 (m, 2H) 2.01-2.32 (m, 7 H) 1.13-1.59 (m, 6 H)

EM (directo): 687 (M+1)

EJEMPLO 52

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(9a*S* o 9a*R*)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E52-Enantiómero 2)



El compuesto del título se obtuvo como el segundo compuesto, etiquetado como el enantiómero 2, a partir de la separación quiral realizada en 2-[3,5-Bis(trifluorometil)fenil]-*N*-[6-(2,2-dioxidohexahidropirazino[2,1-*c*][1,4]

580

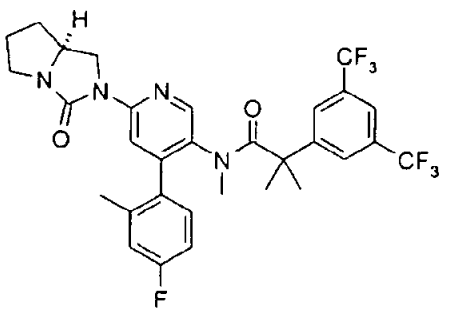
tiazin-8(1*H*)-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E33) como se reportó para 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(9a*R* o 9a*S*)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E51) (se obtuvieron 70 mg, >95.5%e.e., tiempo de retención analítico 14.56 min).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (br. s., 1H) 7.89 (br. s., 1H) 7.61- 7.84 (m, 2H) 7.16 (d, 1H) 6.90-7.14 (m, 2H) 6.72 (br. s., 1H) 4.12-4.31 (m, 2H) 3.08-3.32 (m, 5 H) 2.85-3.03 (m, 3 H) 2.52-2.73 (m, 2H) 2.01-2.32 (m, 7 H) 1.13-1.59 (m, 6 H).

EM (directo): 687 (M+1)

EJEMPLO 53

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7a*S*)-3-oxotetrahidro-1*H*-pirrolo[1,2-*c*]imidazol-2(3*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E53)



La 2-[3,5-bis(trifluorometil)fenil]-*N*-(4-(4-fluoro-2-metilfenil)-6-{[(2*S*)-2-pirrolidinilmetil]amino}-3-piridinil)-*N*,2-dimetilpropanamida de partida (D62, 38 mg, 0.064 mmoles) se disolvió en 1 ml de diclorometano anhidro y se

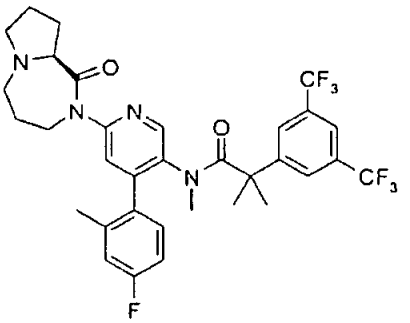
trató con trietilamina (20 µl, 0.143 mmoles). La solución se llevó a 0°C y se añadió trifosgeno (10 mg, 0.034 mmoles). La reacción se agitó a 0°C durante 15 min, después se llevó a temperatura ambiente. Después de 24 hr, la reacción se diluyó con diclorometano (10 ml) y se extrajo con salmuera. Los compuestos orgánicos se recogieron y el solvente se removió. El producto se aisló por cromatografía instantánea (sílice, ciclohexano: EtOAc 80:20 a EtOAc). De esta manera se obtuvieron 8 mg del compuesto objetivo.

CLAR/EM: m/z= 623 (M+1),

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.03 (s, 1H) 8.00 (s, 1H) 7.89 (s, 1H) 7.66-7.72 (m, 2H) 7.04-7.13 (m, 2H) 6.94-7.04 (m, 1H) 4.10 (t, 1H) 3.94 (dd, 1H) 3.74-3.84 (m, 1H) 3.47-3.59 (m, 1H) 2.90-3.08 (m, 1H) 2.43 (s, 3 H) 2.09 (s, 3 H) 1.97-2.10 (m, 1H) 1.74-1.98 (m, 2H) 1.47-1.73 (m, 1H) 1.36 (s, 6 H)

EJEMPLO 54

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*S*)-1-oxohexahidro-1*H*-pirrolo[1,2-*a*][1,4]diazepin-2(3*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E54)



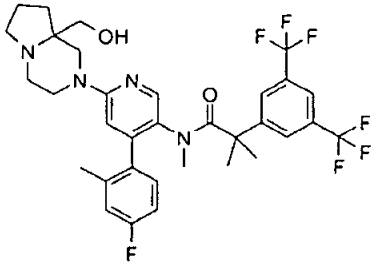
Una solución de (9a*S*)-octahidro-1*H*-pirrolo[1,2-*a*][1,4]diazepin-1-ona (Polish Journal of Chemistry, 59(10-12), 1243-6; 1985) (31 mg, 0.201 mmoles), 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (53 mg, 0.0996 mmoles), N,N'-dimetietilendiamina (22 µl, 0.207 mmoles), yoduro de cobre(I) (38 mg, 0.200 mmoles) y carbonato de cesio (65 mg, 0.199 mmoles) en 3 ml de dioxano se calentó a 100°C en un vial sellado durante la noche. El calentamiento se continuó durante 2 días más. Se diluyó con 10 ml de EtOAc y se extrajo con agua. Los compuestos orgánicos se secaron (Na_2SO_4) y el solvente se removió. El producto se aisló por cromatografía instantánea (sílice, ciclohexano:EtOAc 90:10 a 30:70). Se obtuvieron así 14 mg del compuesto objetivo.

CLAR/EM: m/z= 651 (M+1), >99% por UV.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.34 (s, 1H) 8.10 (s, 1H) 7.84 (br. s., 2H) 7.77 (br. s., 1H) 7.57 (s, 1H) 7.25 (d, 1H) 7.19 (br. s., 1H) 4.54 (br. s., 1H) 3.96 (t, 1H) 3.72 (dd, 1H) 3.25 (dd, 1H) 3.02-3.09 (m, 1H) 2.53-2.67 (m, 1H) 2.43 (s, 3 H) 2.28-2.42 (m, 1H) 2.19 (s, 3 H) 1.81-1.91 (m, 1H) 1.66-1.78 (m, 2H) 1.60 (s, 3 H) 1.44 (s, 3 H) 1.26-1.38 (m, 1H) 1.11-1.22 (m, 1H) 0.89-1.07 (m, 1H)

EJEMPLO 55

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[8a-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E55)



A una solución de hexahidropirrolo[1,2-*a*]pirazin-8a(6*H*)-ilmetanol (D67, 35 mg) en sulfóxido de dimetilo (1.5 ml), se añadieron 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (60 mg) y carbonato de potasio (63 mg). La mezcla resultante se calentó a 150°C durante 24 horas. La mezcla se dejó enfriar a t.a. y D67 adicional (17 mg) y carbonato de potasio (15 mg) se añadieron. La mezcla resultante se calentó a 150°C durante 8 horas adicionales y después se dejó enfriar a t.a. y se diluyó con agua (2 ml). La fase acuosa se extrajo con acetato de etilo (3 x 2.5 ml). Los extractos orgánicos combinados se secaron y se concentraron bajo vacío a un residuo que se purificó dos veces por cromatografía instantánea (primera purificación: EtOAc/Cycl a partir de 80/20 a 100:0 después DCM/MeOH 95:5. Segunda purificación: DCM/MeOH 98:2) para dar el compuesto deseado (7.7 mg) como espuma amarilla.

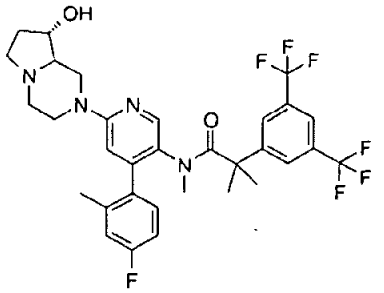
CCD: DCM/MeOH 9:1, Rf=0.29.

UPLC/MS: pico a Tr = 0.673 min con m/z = 653 $[M+H]^+$.

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 7.94 (s, 1H) 7.82 (br. s., 1H) 7.73 (s, 2H) 7.07-7.20 (m, 2H) 6.96-7.07 (m, 1H) 6.46 (s, 1H) 3.90 (d, 1H) 3.37-3.60 (m, 3 H) 3.11-3.32 (m, 4 H) 2.80-2.95 (m, 2H) 2.47 (s, 3 H) 2.18 (s, 3 H) 1.61-1.82 (m, 2H) 1.40 (s, 6 H) 1.32-1.54 (m, 2H).

EJEMPLO 56

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8*S*)-8-hidroxihexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E56)



A una solución de (8*S*)-octahidropirrolo[1,2-*a*]pirazin-8-ol (D71, 32 mg) en sulfóxido de dimetilo (1.2 ml), se añadieron 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (60 mg) y carbonato de potasio (63 mg). La mezcla resultante se calentó a 150°C durante 24 horas. La mezcla se dejó enfriar a t.a. y se diluyó con agua (2 ml). La fase acuosa se extrajo con acetato de etilo (3 x 2.5 ml). Los extractos orgánicos combinados se secaron y

se concentraron bajo vacío a un residuo que se purificó por cromatografía instantánea (DCM/MeOH a partir de 100:0 a 95:5) para dar el compuesto deseado (18.8 mg) como espuma amarilla.

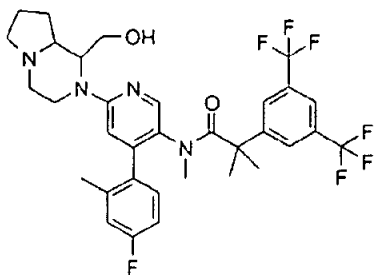
CCD: DCM/MeOH 9:1, Rf=0.48.

UPLC/MS: pico a Tr = 0.71 min con m/z = 639 $[M+H]^+$.

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 7.95 (s, 1H) 7.86 (br. s., 1H) 7.74 (s, 2H) 7.07-7.20 (m, 2H) 6.98-7.08 (m, 1H) 6.59 (s, 1H) 4.12-4.35 (m, 3 H) 2.82-2.99 (m, 3 H) 2.48 (s, 3 H) 2.43-2.66 (m, 2H) 2.24-2.39 (m, 1H) 2.18 (s, 3 H) 2.06-2.24 (m, 1H) 1.91-2.03 (m, 1H) 1.77-1.89 (m, 1H) 1.51-1.70 (m, 1H) 1.41 (s, 6 H)

EJEMPLO 57

cis-2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[1-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E57)



A una solución de *cis*-2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D74.10.5 mg) en

metanol seco (1 ml) a 0°C, se añadió una gota de HCl concentrado. La mezcla resultante se agitó a 0°C durante 1.5 horas y después se dejó alcanzar t.a. y se agitó a esta temperatura durante 2 horas. La solución después se cargó directamente en un cartucho de SCX (eluyendo con MeOH y amoniaco, solución 0.5N en metanol) para dar el compuesto deseado (4.5 mg) como aceite amarillo.

UPLC/MS: pico a Tr = 0.73 min con m/z = 653 $[M+H]^+$.

Los siguientes ejemplos se obtuvieron mediante preparación análoga a la siguiente:

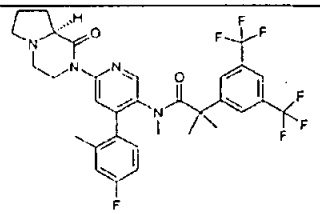
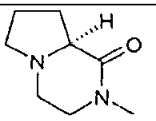
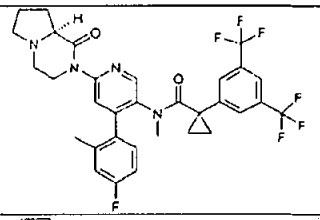
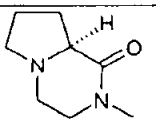
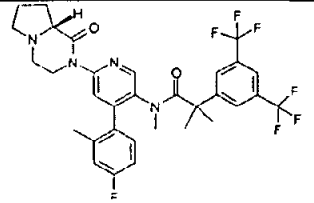
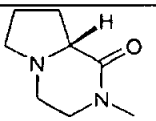
E58

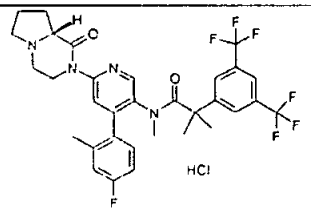
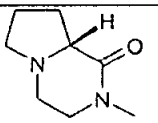
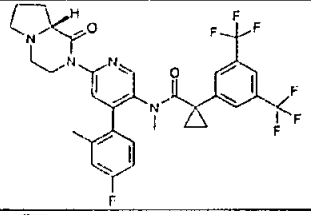
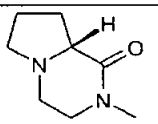
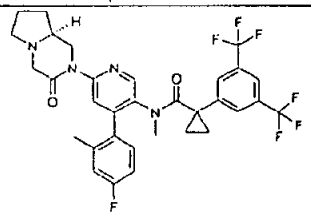
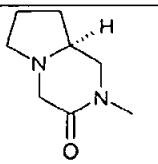
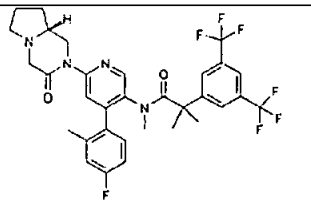
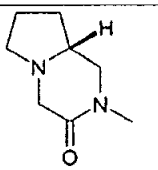
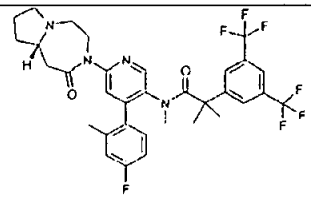
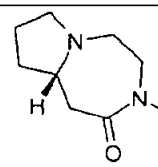
Una suspensión de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (100 mg), (8a*S*)-hexahidropirrolo[1,2-*a*]pirazin-1(2*H*)-ona (D76, 79 mg, 3 eq), CuI (72 mg, 2 eq), N,N'-dimetiletilenodiamina (40 µl, 2 eq) y $CsCO_3$ (122.4 mg, 2 eq) en dioxano (3 ml) se calentó en un tubo sellado a 80°C durante 4 hr y a 120°C durante la noche. La mezcla de reacción se recogió con diclorometano y se lavó con NH_4Cl ac. La fase orgánica se evaporó a sequedad y el crudo se purificó por cromatografía (cartucho de sílice, ciclohexano: EtOAc 1:1 a 0:1) para dar el compuesto del título (39 mg).

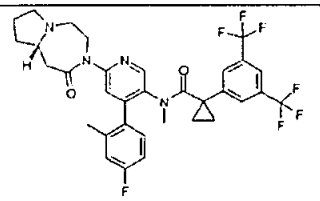
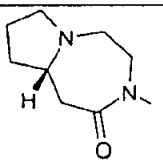
Donde se prepararon, las sales de HCl se prepararon de conformidad con el siguiente procedimiento experimental:

E61

A una solución de 2-[3,5-bis(thfluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(8a*R*)-1-oxohexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-N,2-dimetilpropanamida (E60, 47 mg, 0.074 mmoles) en diclorometano (1.9 ml), enfriada a 0°C, se añadió gota a gota HCl 1 N en Et_2O (88 µl) y la mezcla de reacción se agitó a 0°C durante 30 min. El solvente se evaporó y el sólido se trituró con pentano para dar compuesto del título (50 mg).

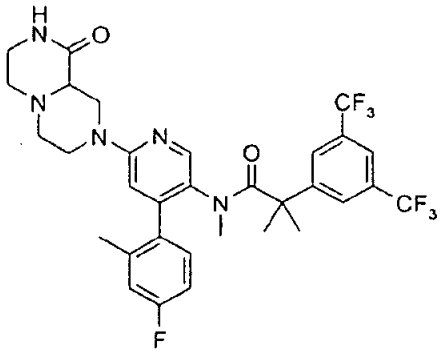
No. de ej.	Estructura	Caracterización	Monómero	Preparación de monómero
E58				**Descripción 76** (8a*S*)-hexa-hidropirrolo[1,2-*a*]pirazin-1(2*H*)-ona **(D76)**
E59				El mismo que el anterior
E60				Descrito en la literatura: Quinolinone compounds. Jpn. Kokai Tokio Koho (1985), 12 pp. CODEN: JKXXAF JP 60166681 A2 19850829 Showa, CAN 104: 109495 AN 1986: 109495 CAPLUS

E61		1H RMN (500 MHz, DMSO-d_6) δ ppm 11.17 (br. S., 1H) 8.35 (s, 1H) 8.04 (s, 1H) 7.83 (s, 1H) 7.69-781 (m, 2H) 7.22 (d, 1H) 7.09-7.17 (m, 2H) 3.09-4.75 (m, 7H) 2.45-2,56 (m, 3H) 2.13 (s, 3H) 1.76-2.45 (m, 4H) 1.11-1.71 (m, 6H)		El mismo que el anterior
E62				El mismo que el anterior
E63				**Descripción 12** (8a*S*)-Hexahidropirrol[1,2-*a*]pirazin-3(4*H*)-ona **(D12)**
E64				**Descripción 14** (8a*R*)-Hexahidropirrolo[1,2-a]pirazin-3(4*H*)-ona **(D14)**
E65				**Descripción 5** (9a*S*)-Hexahidro-1*H*-pirrolo[1,2-*d*][1,4]diazepin-2(3*H*)-ona **(D5)**

E66				**Descripción 5** (9a*S*)-Hexahidro-1*H*-pirrolo[1,2-*d*][1,4]diazepin-2(3*H*)-ona **(D5)**

EJEMPLO 67

2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(9-oxooctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida (E67)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (50 mg, 0.092 mmoles) en 0.5 ml de DMSO se añadió hexahidro-2*H*-pirazino[1,2-*a*]pirazin-1(6*H*)-ona (D78, 33 mg, 0.213 mmoles) y carbonato de potasio (39 mg, 0.28 mmoles) y la reacción se dejó a 150°C durante 24 hr. Se trató diluyendo con diclorometano y extrayendo con salmuera. Los compuestos orgánicos se secaron ($Na2SO_4$), y el solvente se removió. El producto se purificó por cromatografía instantánea: sílice, ciclohexano:EtOAc 50:50 a

590

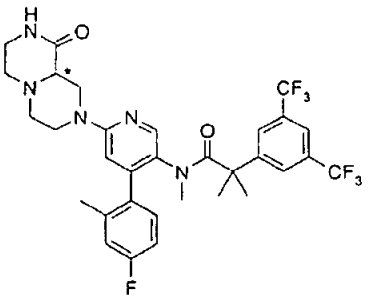
EtOAc. Se obtuvieorn 37 mg del compuesto del título.

EM (directo): 652 (M+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.92 (s, 1H) 7.82 (d, 1H) 7.66-7.78 (m, 2H) 6.92-7.20 (m, 3 H) 6.64 (br. s., 1H) 4.57-4.70 (m, 1H) 3.25-3.32 (m, 1H) 3.01-3.13 (m, 1H) 2.83-2.96 (m, 3 H) 2.52-2.68 (m, 2H) 2.40 (dt, 1H) 2.01-2.31 (m, 8 H) 1.14-1.59 (m, 6 H)

EJEMPLO 68

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)- 6-[(9a*R* o 9a*S*)-9-oxooctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E68-Enantiómero 1)



2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(9-oxooctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida (E67, 30 mg) se sometió a separación quiral para aislar sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual se aisló usando las siguientes condiciones (obtenidos 8.3 mg, 75%e.e., tiempo de retención analítico 15.5 min).

Condiciones preparativas:

Cantidad suministrada	30 mg
Columna quiral	CHIRALCEL OD-H, (25 x 2.1) cm
Fase móvil	n-Hexano/2-propanol 87/13% v/v
Velocidad de flujo	22 ml/min
P	182 bar
T	36 C
Detección	UV a 220 nm

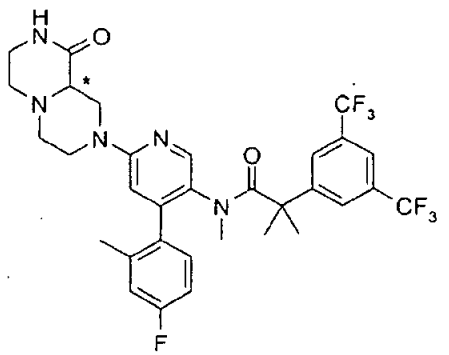
Condiciones analíticas SFC (Berger):

Columna quiral	CHIRALCEL OD-H, (25 x 0.46) cm
Fase móvil	n-Hexano/2-propanol 85/15% v/v
Velocidad de flujo	1.5 ml/min
P	182 bar
T	35 C
Detección	UV a 220 nm

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.03 (s, 1H) 7.92 (s, 1H) 7.82 (d, 1H) 7.50-7.78 (m, 2H) 6.90-7.21 (m, 3 H) 6.66 (br. s., 1H) 4.48-4.78 (m, 1H) 4.05-4.21 (m, 1H) 3.21-3.46 (m, 1H) 3.04-3.11 (m, 1H) 2.79-2.96 (m, 3 H) 2.55-2.67 (m, 2H) 2.38 (dd, 1H) 1.98-2.31 (m, 7 H) 1.07-1.64 (m, 6 H)

EJEMPLO 69

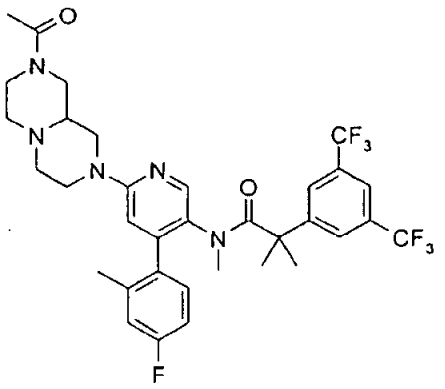
2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*S* o 9a*R*)-9-oxooctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E69-Enantiómero 2)



El compuesto del título se obtuvo como el enantiómero etiquetado como 2 a partir de separación quiral de 2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(9-oxooctahidro-2*H*-pirazino [1,2-*a*]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida (E67), como se describió para 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*R* o 9a*S*)-9-oxooctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E68 - Enantiómero 1). Obtenidos 3.8 mg, >95.5%e.e., tiempo de retención analítico 17.7 min).

EJEMPLO 70

N-[6-(8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E70)



A una solución de crudo 2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida (preparado con un procedimiento análogo a aquel descrito para D80, 89 mg, 0.14 mmoles) en 5 ml de diclorometano se añadieron a 0°C trietilamina (197 µl, 1.41 mmoles) y cloruro de acetilo (75 µl, 1.0 mmoles). La reacción se dejó a temperatura ambiente durante 2 hr. Se diluyó con diclorometano, se extrajo con solución de $NaHCO_3$ saturada, los compuestos orgánicos se secaron (Na_2SO_4), y el solvente se removió. El producto se purificó por cromatografía instantánea (sílice, ciclohexano: EtOAc 50:50 a EtOAc). Se obtuvieron 60 mg.

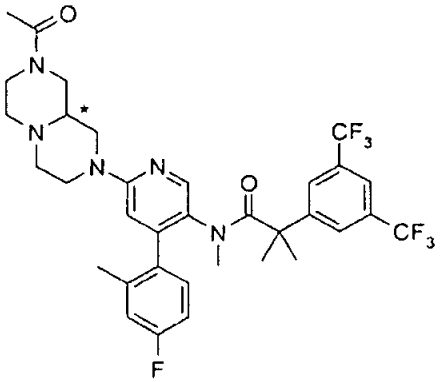
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.89 (s, 1H) 7.61-7.83 (m, 2H) 7.14 (d, 1H) 6.92-7.21 (m, 2H) 6.65-6.80 (m, 1H) 4.05-4.53 (m, 3 H) 3.81 (dd, 1H) 2.72-2.97 (m, 4 H) 2.59-2.70 (m, 2H) 2.50 (s, 3 H) 1.99

(s, 3 H) 1.78-2.37 (m, 6 H) 1.01-1.56 (m, 6 H)

EM (directo): m/z= 680 (M+1), 340 (2M+2)/2.

EJEMPLO 71

_N_-[6-[(9a*R* o 9a*S*)-8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E71- Enantiómero 1)



N-[6-(8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E70, 44.5 mg) se sometió a separación quiral para aislar sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual se aisló usando las siguientes condiciones (obtenidos 12.8 mg, >99.5%e.e., tiempo de retención analítico 13.1 min)

Condiciones preparativas:

Cantidad suministrada	44.5 mg
Columna quiral	CHIRALCEL OD-H, (25 x 2.1) cm
Fase móvil	n-Hexano/2-propanol 85/15% v/v
Velocidad de flujo	22 ml/min
P	182 bar
T	36 C
Detección	UV a 220 nm

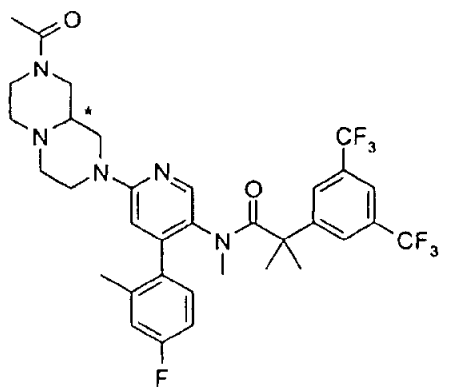
Condiciones analíticas SFC (Berger):

Columna quiral	CHIRALCEL OD-H, (25 x 0.46) cm
Fase móvil	n-Hexano/2-propanol 85/15% v/v
Velocidad de flujo	1.5 ml/min
P	180 bar
T	35 C
Detección	UV a 220 nm

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.89 (s, 1H) 7.61-7.83 (m, 2H) 7.14 (d, 1H) 6.92-7.21 (m, 2H) 6.65-6.80 (m, 1H) 4.05-4.53 (m, 3 H) 3.81 (dd, 1H) 2.72-2.97 (m, 4 H) 2.59-2.70 (m, 2H) 2.50 (s, 3 H) 1.99 (s, 3 H) 1.78-2.37 (m, 6 H) 1.01-1.56 (m, 6 H)

EJEMPLO 72

N-[6-[(9a*S* o 9a*R*)-8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E72- Enantiómero 2)

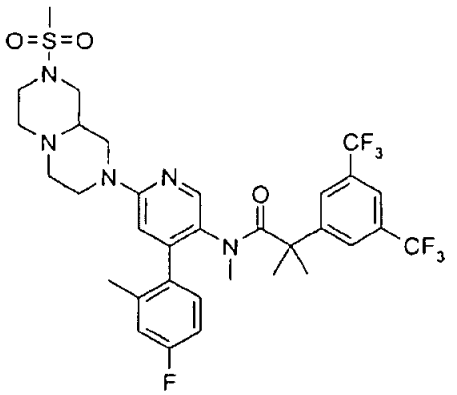


El compuesto del título se obtuvo como el enantiómero etiquetado como 2 a partir de separación quiral de *N*-[6-(8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis (trifluorometil)fenil]-*N*,2-dimetilpropanamida (E70), como se describió para *N*-[6-[(9a*R* o 9a*S*)-8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E71- Enantiómero 1). Obtenidos 11.6 mg, >95.5%e.e., tiempo de retención analítico 17.5 min)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.89 (s, 1H) 7.61-7.83 (m, 2H) 7.14 (d, 1H) 6.92-7.21 (m, 2H) 6.65-6.80 (m, 1H) 4.05-4.53 (m, 3 H) 3.81 (dd, 1H) 2.72-2.97 (m, 4 H) 2.59-2.70 (m, 2H) 2.50 (s, 3 H) 1.99 (s, 3 H) 1.78-2.37 (m, 6 H) 1.01-1.56 (m, 6 H)

EJEMPLO 73

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[8-(metilsulfonil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E73)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida cruda (D80, 100 mg, 0.16 mmoles) en 5 ml de diclorometano se añadieron trietilamina (44 µl, 0.32 mmoles, 2 eq.) y, a 0°C, cloruro de metansulfonilo (18 µl, 0.24 mmoles, 1.5 eq.). La reacción se dejó a temperatura ambiente durante la noche. Se añadieorn 3 equivalentes adicionalmes de cloruro de metansulfonilo. Después se diluyó con diclorometano, se extrajo con $NaHCO_3$ saturado, los compuestos orgánicos se secaron (Na_2SO_4), y el solvente se removió. El producto se purificó por cromatografía instantánea (sílice, EtOAc). Se obtuvieron 60 mg del compuesto del título.

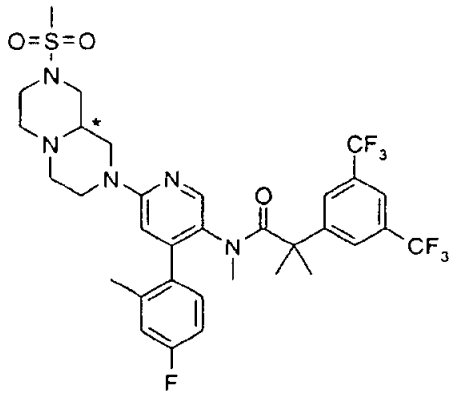
EM (directo): m/z= 716 (M+1).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.89 (s, 1H)

7.63-7.81 (m, 2H) 6.92-7.22 (m, 3 H) 6.77 (s, 1H) 4.25-4.41 (m, 1H) 4.13-4.31 (m, 1H) 3.51 (d, 1H) 3.45 (d, 1H) 2.88 (s, 3 H) 2.81-2.92 (m, 2H) 2.50 (s, 3 H) 2.40-2.62 (m, 3 H) 2.18 (s, 3 H) 2.05-2.28 (m, 4 H) 1.49 (s, 3 H) 1.35 (s, 3 H)

EJEMPLO 74

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*R* o 9a*S*)-8-(metilsulfonil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E74 - Enantiómero 1)



N-[6-(8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E73, 55.5 mg) se sometió a separación quiral para aislar sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual se aisló usando las siguientes condiciones (se obtuvieron 11.5 mg, >99.5%e.e., tiempo de retención analítico 8.16 min)

Condiciones preparativas:

Cantidad suministrada	55.5 mg
Columna quiral	Chiralpak AD-H, (25 x 2.1) cm
Fase móvil	n-Hexano/etanol 60/40% v/v
Velocidad de flujo	13 ml/min

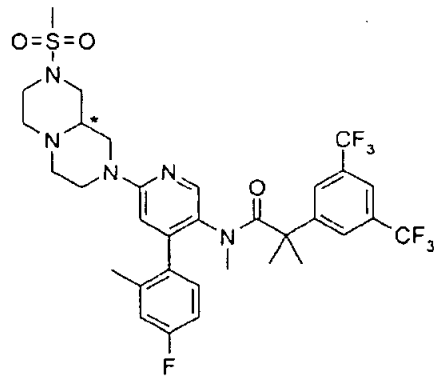
Condiciones analíticas:

Columna quiral	Chiralpak AD-H, (25 x 0.46) cm
Fase móvil	n-Hexano/etanol 60/40% v/v + 1% de isopropilamina
Velocidad de flujo	0.8 ml/min
Detección	UV 200-400 nm

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.90 (s, 1H) 7.59-7.82 (m, 2H) 6.87-7.20 (m, 3 H) 6.68-6.84 (m, 1H) 4.28-4.40 (m, 1H) 4.17-4.27 (m, 1H) 3.52 (d, 1H) 3.46 (d, 1H) 2.90 (s, 3 H) 2.80-2.93 (m, 4 H) 2.44-2.57 (m, 5 H) 2.01-2.27 (m, 6 H) 1.24-1.60 (m, 6 H)

EJEMPLO 75

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*S* o 9a*R*)-8-(metilsulfonil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E75 - Enantiómero 2)

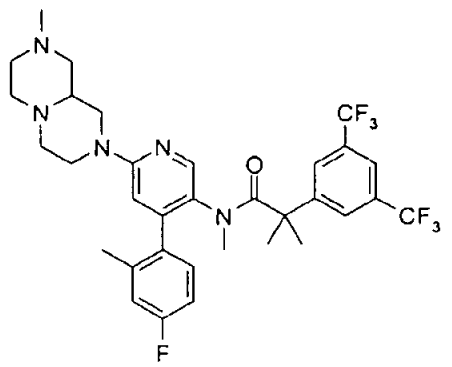


El compuesto del título se obtuvo como el enantiómero etiquetado como 2 a partir de separación quiral de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[8-(metilsulfonil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E73), como se describió para 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*R* o 9a*S*)-8-(metilsulfonil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E74 Enantiómero 1). Se obtuvieron 12.6 mg, >95.5%e.e., tiempo de retención analítico 14.36 min).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.90 (s, 1H) 7.59-7.82 (m, 2H) 6.87-7.20 (m, 3 H) 6.68-6.84 (m, 1H) 4.28-4.40 (m, 1H) 4.17-4.27 (m, 1H) 3.52 (d, 1H) 3.46 (d, 1H) 2.90 (s, 3 H) 2.80-2.93 (m, 4 H) 2.44-2.57 (m, 5 H) 2.01-2.27 (m, 6 H) 1.24-1.60 (m, 6 H)

EJEMPLO 76

2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(8-metiloctahidro-2*H*-pirazino[1,2-a]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida (E76)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida cruda (D80, 100 mg, 0.16 mmoles) en 5 ml de acetonitrilo se añadió una solución de formaldehído acuosa al 37% (24 µl, 0.32 mmoles). La solución se agitó a temperatura ambiente durante 30 min, y después se añadió triacetoxiborhidruro de sodio (50 mg, 0.24 mmoles) y la reacción se agitó a temperatura ambiente durante la noche. El solvente se evaporó y el residuo se disolvió en diclorometano y se extrajo con agua y salmuera. El producto se purificó por cromatografía instantánea (sílice, diclorometano a diclorometano:MeOH 95:5). Se obtuvieron 58 mg del compuesto del título.

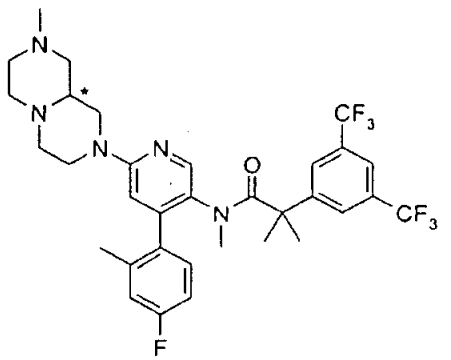
EM (directo): m/z= 652 (M+1).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.96-8.08 (m, 1H) 7.81-7.93 (m, 1H) 7.60-7.80 (m, 2H) 7.15 (d, 1H) 6.88-7.12 (m, 2H) 6.60-6.79 (m, 1H)

4.24 (d, 1H) 4.12 (d, 1H) 2.74-2.92 (m, 2H) 2.61-2.73 (m, 2H) 2.41-2.57 (m, 4 H) 1.92-2.31 (m, 11H) 1.68 (t, 1H) 1.10-1.56 (m, 6 H)

EJEMPLO 77

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*S* o 9a*R*)-8-metiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E77 - Enantiómero 1)



N-[6-(8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E76, 50 mg) se sometió a separación quiral para aislar sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual se aisló usando las siguientes condiciones (se obtuvieron 13 mg, 70%e.e., tiempo de retención analítico 10.7 min).

Condiciones semipreparativas SFC (Gilson):

Cantidad suministrada	50 mg
Columna quiral	CHIRALCEL OD-H, (25 x 2.1) cm
Fase móvil	n-Hexano/(etanol+0.1% de isopropilamina) 95/5% v/v
Velocidad de flujo	22 ml/min
P	182 bar
T	36 C
Detección	UV a 220 nm

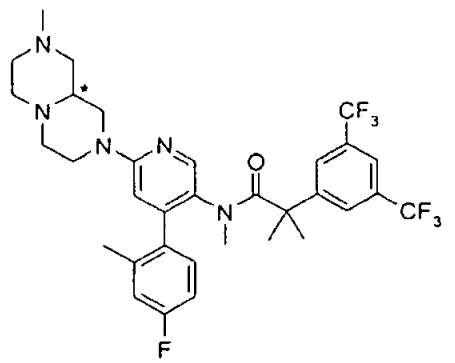
Condiciones analíticas SFC (Berger):

Columna quiral	CHIRALCEL OD-H, (25 x 0.46) cm
Fase móvil	n-Hexano/2-propanol 85/15% v/v
Velocidad de flujo	1.5 ml/min
P	180 bar
T	35 C
Detección	UV a 220 nm

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.96-8.07 (m, 1H) 7.84-7.91 (m, 1H) 7.61-7.81 (m, 2H) 7.16 (d, 1H) 6.99-7.13 (m, 2H) 6.65-6.73 (m, 1H) 4.24 (d, 1H) 4.13 (d, 1H) 2.73-2.94 (m, 2H) 2.62-2.75 (m, 2H) 2.37-2.58 (m, 4 H) 1.95-2.33 (m, 11 H) 1.69 (t, 1H) 1.25-1.56 (m, 6 H).

EJEMPLO 78

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*R* o 9a*S*)-8-metiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetilpropanamida (E78 - Enantiómero 2)

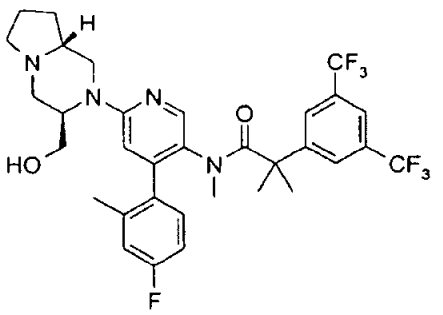


El compuesto del título se obtuvo como el enantiómero etiquetado como 2 a partir de separación quiral de 2-[3,5-bis(trifluorometil)fenil]-*N*-[4-(4-fluoro-2-metilfenil)-6-(8-metiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-3-piridinil]-*N*,2-dimetilpropanamida (E76), como se describió para 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(9a*S* o 9a*R*)-8-metiloctahidro-2*H*-pirazin[1,2-*a*]pirazin-2-il]-3-piridinil}-*N*,2-dimetil-propanamida (E77 - Enantiómero 1). Se obtuvieron 12 mg, >95.5%e.e., tiempo de retención analítico 13.9 min).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.96-8.07 (m, 1H) 7.84-7.91 (m, 1H) 7.61-7.81 (m, 2H) 7.16 (d, 1H) 6.99-7.13 (m, 2H) 6.65-6.73 (m, 1H) 4.24 (d, 1H) 4.13 (d, 1H) 2.73-2.94 (m, 2H) 2.62-2.75 (m, 2H) 2.37-2.58 (m, 4 H) 1.95-2.33 (m, 11 H) 1.69 (t, 1H) 1.25-1.56 (m, 6 H)

EJEMPLO 79

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*R*,8a*R*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E79)



(3*R*,8a*R*)-octahidropirrolo[1,2-*a*]pirazin-3-ilmetanol (190 mg, 1.22 mmoles, Tetrahedron Asymmetry, 1996, 7(7), 1999-2005) se disolvió en 10 ml de tolueno, seguido por la 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (323 mg, 0.607 mmoles), 2-diciclohexilfosfin-2'-(*N*,*N*-dimetilamino)bifenilo (ligando) (57 mg, 0.144 mmoles), $Pd(dba)_2$ (35 mg, 0.061 mmoles) y, por último, carbonato de cesio (297 mg, 0.912 mmoles). La mezcla se agitó a 130°C. Después de 3.5 hr, se añadieron más ligando (55 mg, 0.139 mmoles) y $Pd(dba)_2$ (35 mg, 0.061 mmoles) y la reacción se dejó durante la noche. Se dejó enfriar a temperatura ambiente, se diluyó con 10 ml de MeOH, se cargó sobre una columna de SCX 10g, se lavó con MeOH y se eluyó con amoniaco metanólico 1 M. La muestra que venía de la columna de SCX se purificó adicionalmente por cromatografía instantánea: 1a. columna: sílice, ciclohexano: EtOAc 50:50 a 0:100; 2a. columna, sílice NH_2-modificada, ciclohexano: EtOAc 100:0 a

0:100. Se aislaron 29 mg del material objetivo.

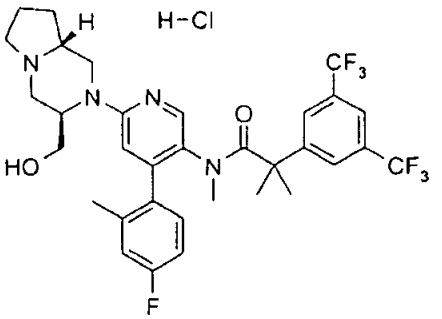
O.A.CLAR, pico a 5.20 min, >99% de pureza (UV).

CL/EM (verificadod espués de la 1a. columna): m/z= 653.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.85 (s, 1H) 7.74 (br. s., 2H) 7.15 (d, 1H) 7.05-7.13 (m, 2H) 6.53 (s, 1H) 3.94-4.02 (m, 2H) 3.58-3.67 (m, 1H) 3.53-3.59 (m, 1H) 3.08-3.18 (m, 1H) 2.82-2.89 (m, 1H) 2.72-2.80 (m, 1H) 2.50-2.56 (m, 1H) 2.24 (s, 3 H) 2.15-2.19 (m, 1H) 2.10 (s, 3 H) 1.89 (s, 3 H) 1.73-1.83 (m, 1H) 1.47 (s, 3 H) 1.40-1.70 (m, 3 H) 1.34 (s, 3 H)

EJEMPLO 80

Clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*R*,8a*R*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E80)



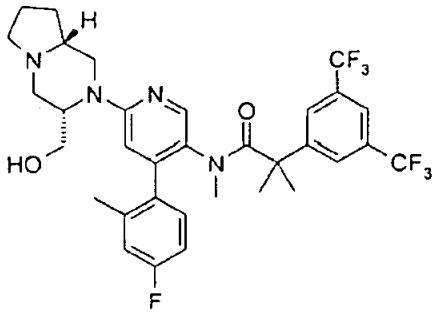
La base libre de partida (E79, 25 mg, 0.038 mmoles) se disolvió en 0.3 ml de diclorometano y se añadió Cl 1M en Et_2O (57 µl, 0.057 mmoles) a 0°C bajo una corriente de nitrógeno. La solución se agitó durante 15 min a 0°C y el solvente se removió bajo una corriente de nitrógeno. El sólido se trituró con Et_2O y pentano, dejando el producto como un sólido blanquecino (25 mg).

O.A.CLAR, pico a 5.20 min, >99% de pureza (UV).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 10.14 (br. s., 1H) 8.03 (s, 1H) 7.92 (s, 1H) 7.75 (br. s., 2H) 7.17 (d, 1H) 7.10 (br. s., 2H) 6.67 (s, 1H) 5.17 (br. s., 1H) 4.24-4.36 (m, 1H) 3.48-4.04 (m, 6 H) 3.07-3.16 (m, 1H) 2.54-2.59 (m, 1H) 2.24 (s, 3 H) 2.17 (s, 3 H) 2.10 (s, 1H) 1.97-2.06 (m, 1H) 1.70-1.89 (m, 3 H) 1.48 (s, 3 H) 1.34 (s, 3 H)

EJEMPLO 81

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*S*,8a*R*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E81)



(3*S*,8a*R*)-Octahidropirrolo[1,2-*a*]pirazin-3-ilmetanol (Tetrahedron Asymmetry, 1996, 7(7), 1999-2005, 230 mg, 1.47 mmoles) y 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-imetilpropanamida [WO 2005/002577] (570 mg, 1.07 mmoles) se disolvieron en 12 ml de tolueno. Se añadieron 2-diciclohexilfosfin-2'-(*N*,*N*-dimetilamino)bifenilo (ligando) (78 mg, 0.20 mmoles), $Pd(dba)_2$ (45 mg, 0.08 mmoles) y, por último, carbonato de cesio (697 mg, 2.14 mmoles). La

recipiente de reacción se selló y se hizo burbujear nitrógeno a trav´´es de la solución durante 15 min. La mezcla de reacción se calentó a 140°C durante 15 hr. La mezcla se diluyó con 100 ml de EtOAc y se extrajo con agua. La fase acuosa se extrajo nuevamente con diclorometano. Los compuestos orgánicos combinados se secaron y el solvente se removió. El producto se purificó por cromatografía instantánea: sílice, ciclohexano: EtOAc 50:50 a 0:100. Purificación adicional por CLAR (condiciones prep.: columna: Gemini C18 5 µm, 100 x 19 mm; Fase móvil: A: sol. de NH_4HCO_3 10 mM, pH 10; B: CH3CN, Gradiente: 50% (B) durante 1 min, de 50% (B) a 65% (B) en 12 min, 95% (B) durante 6 min; Velocidad de flujo: 17 ml/min; Intervalo de longitud de onda de UV: 210-350 nm; Intervalo de masa: 100-900 amu; Ionización: ES+. Se aislaron 31 mg del compuesto del título.

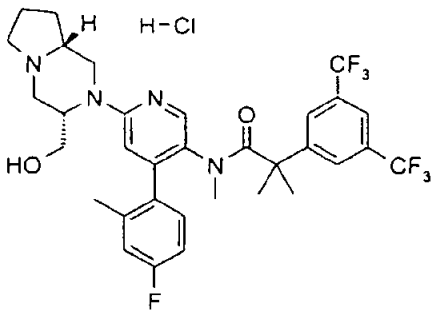
O.A.CLAR, pico a 5.17 min, >99% de pureza (UV).

CL/EM: m/z= 653 (datos analíticos de separación por CLAR).

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 7.90-8.02 (m, 1H) 7.82 (s, 1H) 7.70-7.77 (m, 2H) 7.07-7.23 (m, 2H) 7.03 (td, 1H) 6.58 (s, 1H) 4.42 (dd, 1H) 4.20-4.34 (m, 1H) 3.75 (t, 1H) 3.49 (dd, 1H) 3.31 (d, 1H) 2.97-3.17 (m, 1H) 2.70 (t, 1H) 2.47 (s, 3 H) 2.17 (s, 3 H) 2.12-2.21 (m, 1H) 1.95-2.14 (m, 1H) 1.86-2.07 (m, 1H) 1.61-1.99 (m, 4 H) 1.41 (s, 6 H).

EJEMPLO 82

Clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*S*,8a*R*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E82)



2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*S*, 8a*R*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E81, 25 mg, 0.038 mmoles) se convirtió a su clorhidrato como se reportó antes en el procedimiento para clorhidrato de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*R*,8a*R*)-3-(hidroximetil) hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E80). Se obtuvieron 26 mg del compuesto del título.

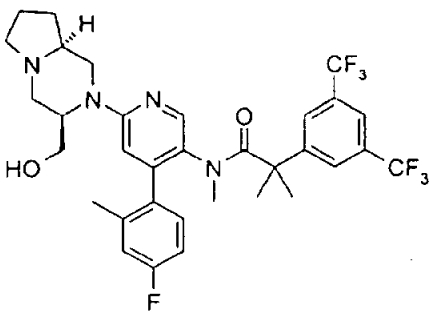
O.A.CLAR, pico a 5.13 min, 98.6% de pureza (UV).

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 10.31 (br. s., 1H) 8.07 (s, 1H) 7.90-7.98 (m, 1H) 7.63-7.87 (m, 2H) 6.97-7.31 (m, 3 H) 6.74 (s, 1H) 4.48-4.95 (m, 2H) 4.02-4.32 (m, 1H) 2.92-4.01 (m, 4 H) 2.27 (s, 3 H) 2.12 (s, 3 H) 1.38 (s, 6 H) 0.66-2.76 (m, 7 H).

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EJEMPLO 83

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*R*,8a*S*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E83)



A una solución de (3*R*,8a*S*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirrolo[1,2-*a*]pirazina (D81, 200 mg, 0.739 mmoles) en 3 ml de tolueno se añadieron 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-N,2-dimetilpropanamida [WO 2005/002577] (304 mg, 0.569 mmoles) $(t\text{-}Bu_3P)_2Pd$ (58 mg, 0.114 mmoles), una solución acuosa al 25% de cloruro de cetiltrimetilamonio (35 µl), y, por último, NaOH acuoso al 50% (68 µl). La reacción se desoxigenó mediante dos ciclos de congelamiento-bombeo-descongelamiento y después se calentó a 90°C durante la noche. La solución se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado y salmuera. La muestra se purificó por cromatografía instantánea (sílice, ciclohexano: EtOAc 95:5 a 60:40). Se aislaron 230 mg del intermediario O-TBDMS protegido (UPLC/MS: pak @ 0.89 min, m/z= 767 (M+1), 384 (M+2)/2).

El intermediario se disolvió en 10 ml de MeOH y se añadieron

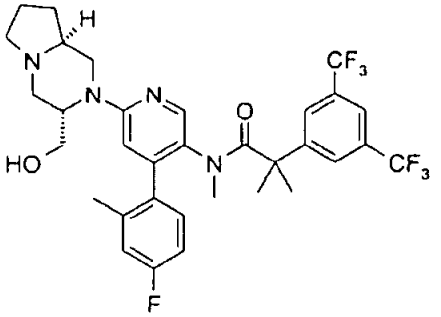
0.5 ml de HCl concentrado. La reacción se dejó a temperatura ambiente durante 1 hr. El producto se aisló pr cartucho de SCX. Se aislaron 133 mg del compuesto del título.

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 7.90-8.02 (m, 1H) 7.82 (s, 1H) 7.70-7.77 (m, 2H) 7.07-7.23 (m, 2H) 7.03 (td, 1H) 6.58 (s, 1H) 4.42 (dd, 1H) 4.20-4.34 (m, 1H) 3.75 (t, 1H) 3.49 (dd, 1H) 3.31 (d, 1H) 2.97-3.17 (m, 1H) 2.70 (t, 1H) 2.47 (s, 3 H) 2.17 (s, 3 H) 2.12-2.21 (m, 1H) 1.95-2.14 (m, 1H) 1.86-2.07 (m, 1H) 1.61-1.99 (m, 4 H) 1.41 (s, 6 H).

UPLC/MS: pico a 0.71 min, m/z= 653 (M+1).

EJEMPLO 84

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(3*S*,8a*S*)-3-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E84)



A una solución de (3*S*,8a*S*)-3-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirrolo[1,2-*a*]pirazina (D82, 157 mg, 0.58 mmoles) en 2.5 ml de tolueno se añadieron 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (238 mg,

0.45 mmoles) $(NBu_3P)_2Pd$ (46 mg, 0.09 mmoles), una solución acuosa al 25% de cloruro de cetiltrimetilamonio (26 µl), y, por último, NaOH acuoso al 50% (54 µl). La reacción se desoxigenó por ciclos de congelamiento-bombeo-descongelamiento y después se calentó a 90°C durante 7 hr. La reacción se verificó por UPLC/MS, mostrando el producto esperado pico a 0.84 min, con m/z= 767 (M+1) y 384 ((M+2)/2). La solución se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado y salmuera. La muestra se purificó por cromatografía instantánea (sílice, ciclohexano: EtOAc 90:10 a 0:100). Se aislaron 251 mg de Intermediario O-TBDMS protegido.

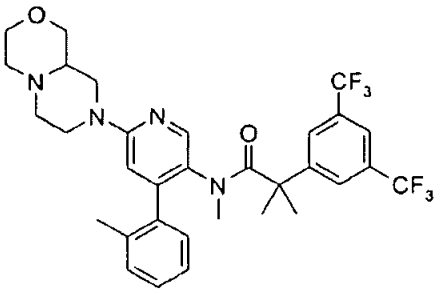
El intermediario se disolvió en 11 ml de MeOH y se añadieron 0.55 ml de HCl concentrado. La reacción se dejó a temperatura ambiente durante 1 hr. El producto se aisló por cartucho de SCX. Se aislaron 140 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.86 (s, 1H) 7.75 (br. s., 2H) 7.15 (d, 1H) 7.10 (br. s., 2H) 6.52 (s, 1H) 4.83 (br. s., 1H) 3.94-4.03 (m, 1H) 3.57-3.69 (m, 1H) 3.50-3.58 (m, 2H) 3.33-3.46 (m, 1H) 3.18-3.27 (m, 1H) 3.10-3.18 (m, 1H) 2.81-2.89 (m, 1H) 2.73-2.81 (m, 1H) 2.51-2.59 (m, 1H) 2.49 (s, 3 H) 2.11 (s, 3 H) 1.84-1.94 (m, 1H) 1.73-1.82 (m, 1H) 1.55-1.68 (m, 1H) 1.46 (s, 3 H) 1.36-1.47 (m, 1H) 1.33 (s, 3 H)

O.A. CLAR: pico a 5.20 min, 98.9% de pureza (UV).

EJEMPLO 85

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E85)



Una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2002/16324A1] (200 mg, 0.388 mmoles), octahidropirazino[2,1-*c*][1,4]oxazina (EP472826, 111 mg, 0.776 mmoles), y carbonato de potasio (161 mg, 1.165 mmoles) en 1 ml de DMSO se calentó a 150°C durante 47 hr. Se trató diluyendo con diclorometano y se extrajo con salmuera. Los compuestos orgánicos se secaron (Na_2SO_4), y el solvente se removió. El producto se purificó por cromatografía instantánea: sílice, diclorometano a diclorometano: MeOH 95:5. Se obtuvieron 92 mg del compuesto del título.

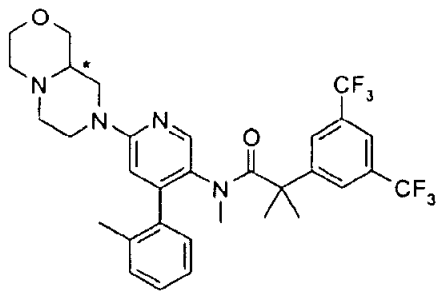
CLAR/EM: Pico a 2.11 min, 621 (M+1)

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.97 (s, 1H) 7.83 (s, 1H) 7.69 (br. s., 2H) 7.23 (s, 2H) 7.15 (br. s., 1H) 7.02 (br. s., 1H) 6.65 (s, 1H) 4.20 (d, 1H) 4.04 (d, 1H) 3.70 (t, 2H) 3.48 (t, 1H) 3.09 (t, 1H) 2.83 (t, 1H) 2.74 (d, 1H) 2.62 (d, 1H) 2.49 (s, 3 H) 2.36 (t, 1H) 2.09-2.24 (m, 3 H) 2.07 (s, 3 H) 1.39 (s, 3 H) 1.25 (s, 3 H).

EJEMPLO 86

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(9a*R* o 9a*S*)-hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida

(E86 - Enantiómero 1)



2-[3,5-bis(trifluorometil)fenil]-*N*-[6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)- il)-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E85, 87 mg) se sometió a separación quiral para aislar sus enantiómeros. El enantiómero etiquetado como 1, de estereoquímica desconocida pero individual se aisló usando las siguientes condiciones (se obtuvieron 41 mg, >99.5%e.e., tiempo de retención analítico 5.84 min)

Condiciones preparativas:

Cantidad suministrada	87 mg
Columna quiral	CHIRALCEL OD, (25 x 2.1) cm
Fase móvil	n-Hexano/2-propanol 94/6% v/v
Velocidad de flujo	18 ml/min
Detección	UV a 225 nm

Condiciones analíticas:

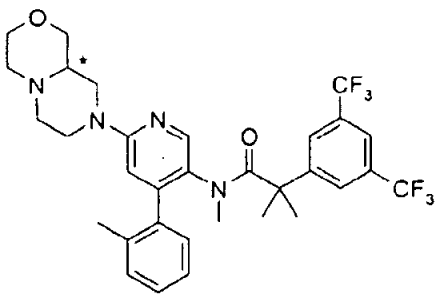
Columna quiral	CHIRALCEL OD-H, (25 x 0.46) cm
Fase móvil	n-Hexano/2-propanol 85/15% v/v
Velocidad de flujo	1.0 ml/min
P	180 bar
T	35 C
Detección	UV a 225 nm

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.87 (s, 1H) 7.64-7.79 (m, 2H) 6.98-7.33 (m, 4 H) 6.64-6.74 (m, 1H) 4.24 (d, 1H) 4.09 (d, 1H) 3.74 (t, 2H) 3.53 (t, 1H) 3.13 (t, 1H) 2.86 (t, 1H) 2.78 (d, 1H) 2.66 (d, 1H) 2.51 (s, 3 H) 2.40 (t, 1H) 2.00-2.30 (m, 6 H) 1.11-1.48 (m, 6 H).

EJEMPLO 87

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(9a*S* o 9a*R*)-hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida

(E87 - Enantiómero 2)



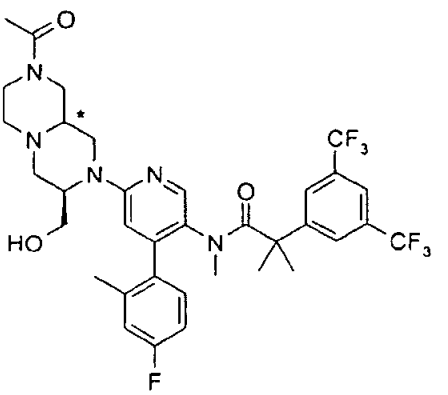
El compuesto del título se obtuvo como el enantiómero etiquetado como 2 a partir de separación quiral de 2-[3,5-bis(trifluorometil) fenil]-*N*-[6-(hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il)-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E85), como se describió para 2-[3,5-

bis(trifluorometil)fenil]-*N*-[6-[(9a*R* o 9a*S*)-hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E86-Enantiómero 1). Se obtuvieron 35 mg del compuesto del título, >95.5%e.e., tiempo de retención analítico 8.80 min.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.87 (s, 1H) 7.64-7.79 (m, 2H) 6.98-7.33 (m, 4 H) 6.64-6.74 (m, 1H) 4.24 (d, 1H) 4.09 (d, 1H) 3.74 (t, 2H) 3.53 (t, 1H) 3.13 (t, 1H) 2.86 (t, 1H) 2.78 (d, 1H) 2.66 (d, 1H) 2.51 (s, 3 H) 2.40 (t, 1H) 2.00-2.30 (m, 6 H) 1.11-1.48 (m, 6 H).

EJEMPLO 88

***N*-[6-[(3*R*, 9a*R* o 9a*S*)-8-acetil-3-(hidroximetil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E88-Diaestereoisómero 1)**



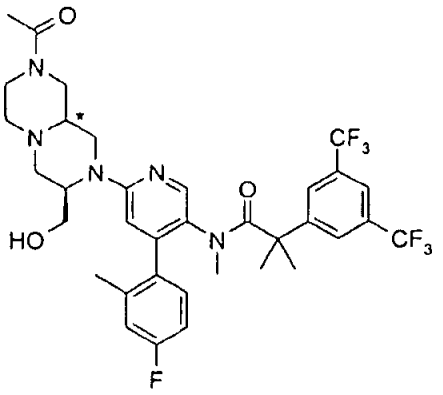
La *N*-[6-((3*R*, 9a*R* o 9a*S*)-8-acetil-3-{[(1,1-dimetiletil)(dimetil)silil]metil}octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (D88, 148 mg) se disolvió en 6 ml de CH_2Cl_2. A esta solución se añadió HCl concentrado (0.3

ml) a 0°C, y se agitó a temperatura ambiente durante 30 min. El análisis de UPLC/MS mostró la conversión completa al producto esperado (pico a 0.70 min, m/z = 710 (M+1), 355.7 ((M+2)/2)). La mezcla de reacción se purificó por cartucho de SCX para dar compuesto del título como un sólido: 106 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.88 (s, 1H) 7.82 (s, 1H) 7.68 (s, 2H) 7.03-7.13 (m, 2H) 6.92-7.01 (m, 1H) 6.63 (s, 1H) 4.40-4.47 (m, 1H) 3.92-4.01 (m, 1H) 3.54-3.65 (m, 2H) 3.51 (dd, 1H) 3.41 (dd, 1H) 3.11 (dd, 1H) 2.72-2.81 (m, 1H) 2.47 (s, 3 H) 2.34-2.53 (m, 7 H) 2.11 (s, 3 H) 1.94 (s, 3 H) 1.35 (s, 6 H).

EJEMPLO 89

***N*-[6-[(3*R*, 9a*S* o 9a*R*)-8-acetil-3-(hidroximetil)octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E89 - Diaestereoisómero 2)**



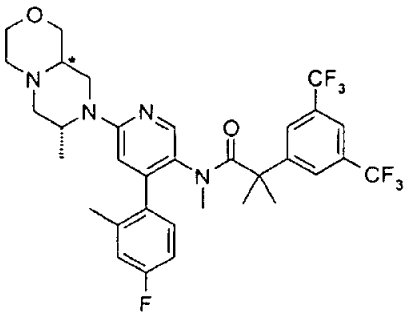
A una solución de la *N*-[6-((3*R*, 9a*S* o 9a*R*)-8-acetil-3-{[(1,1-dimetiletil)dimetil)silil]metil}octahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida

(D92, 199 mg, 0.242 mmoles) en 8 ml de MeOH se añadieron gota a gota 0.4 ml de HCl concentrado. La reacción se agitó a temperatura ambiente durante 3 hr. El asis de UPLC/MS mostró conversión al producto esperado (pico a 0.75 min, m/z = 710 (M+1), 355.7 ((M+2)/2)). La mezcla de reacción se purificó por cartucho de SCX para dar un sólido que se purificó adicionalmente por cromatografía instantánea (sílice, diclorometano a diclorometano: (NH3 0.5 M en MeOH) 95:5). Se obtuvieron 121.6 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.85 (s, 1H) 7.74 (br. s., 2H) 7.15 (d, 1H) 7.10 (br. s., 2H) 6.61 (br. s., 1H) 4.67-4.73 (m, 1H) 4.33 (t, 1H) 4.22 (br. s., 2H) 3.71-3.87 (m, 2H) 3.37-3.45 (m, 1H) 2.98-3.11 (m, 1H) 2.70-2.85 (m, 2H) 2.53-2.69 (m, 2H) 2.49 (s, 3 H) 2.11 (br. s., 3 H) 2.04-2.24 (m, 2H) 1.99 (s, 3 H) 1.84-1.96 (m, 1H) 1.48 (s, 3 H) 1.33 (s, 3 H).

EJEMPLO 90

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)- 6-[(7*R*, 9a*R* o 9a*S*)-7-metilhexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E90 – Diaestereoisómero 1)



A una solución de (7*R*, 9a*R* o 9a*S*)-7-metiloctahidropirazino[2,1-

c][1,4]oxazina (D94, 50 mg, 0.32 mmoles) en 2.1 ml de tolueno se añadió 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (131 mg, 0.246 mmoles), bis-tri-ter-butilfosfinopaladio (25 mg, 0.0492 mmoles), cloruro de hexadeciltrimetilamonio (16 µl de una solución acuosa al 25%) y, por último, solución de hidróxido de sodio (29.5 µl de una solución acuosa al 50%). La solución se desgasificó mediante tres ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C durante 2 hr. Se verificó por UPLC/MS, que mostró picos para el producto esperado a 0.75 min. (m/z = 653 (M+1), 327 (M+2)/2). La solución se diluyó con EtOAc, se extrajo con $NaHCO_3$ saturado y se secó (Na_2SO_4). El producto se aisló por cromatografía instantánea (ciclohexano: EtOAc 70:30 a 0:100, después a EtOAc:MeOH 95:5), obteniendo 74 mg del compuesto del título.

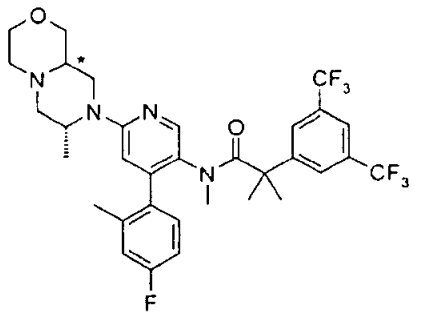
CLAR: Pico a 5.30 min, 98% de pureza (UV).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.03 (s, 1H) 8.01 (s, 1H) 7.74 (br. s., 2H) 7.15 (d, 1H) 7.10 (br. s., 2H) 6.77 (s, 1H) 3.72 (br. s., 1H) 3.65 (d, 1H) 3.55-3.62 (m, 1H) 3.53 (t, 1H) 3.37-3.48 (m, 1H) 3.20 (t, 1H) 2.94-3.01 (m, 1H) 2.77-2.91 (m, 1H) 2.64 (d, 1H) 2.59 (br. s., 3 H) 2.40-2.46 (m, 1H) 2.30-2.38 (m, 1H) 2.09 (s, 3 H) 2.03-2.13 (m, 1H) 1.33 (s, 3 H) 1.13 (br. s., 6H).

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EJEMPLO 91

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*R*, 9a*S* o 9a*R*)-7-metilhexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E91 - Diaestereoisómero 2)



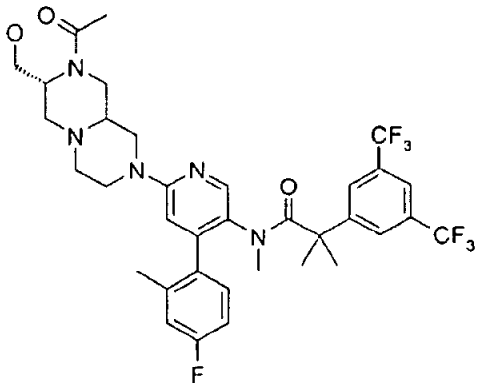
A una solución de (7*R*, 9a*S* o 9a*R*)-7-metiloctahidropirazino[2,1-*c*][1,4]oxazina (D95, 28 mg, 0.18 mmoles) en 1.2 ml de tolueno se añadió 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (73.5 mg, 0.138 mmoles), bis-tri-ter-butilfosfinopaladio (14 mg, 0.028 mmoles), cloruro de hexadeciltrimetilamonio (9 µl de una solución acuosa al 25%) y, por último, solución de hidróxido de sodio (16.5 µl de una solución acuosa al 50%). La solución se desgasificó mediante tres ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C durante 2 hr. Se verificó por UPLC/MS, que mostró picos para el producto esperado a 0.78 min. (m/z = 653 (M+1), 327 (M+2)/2). La solución se diluyó con EtOAc, se extrajo con $NaHCO_3$ saturado y se secó (Na_2SO_4). El producto se aisló por cromatografía instantánea (ciclohexano:EtOAc 100:30 a 0:100), obteniendo 49.6 mg del compuesto del título.

CLAR: Pico a 5.35 min, 98% de pureza (UV).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.87 (s, 1H) 7.74 (br. s., 2H) 7.14 (d, 1H) 7.10 (br. s., 2H) 6.60 (br. s., 1H) 4.49 (br. s., 1H) 3.89-4.01 (m, 1H) 3.70-3.80 (m, 2H) 3.55 (t, 1H) 3.17 (t, 1H) 2.59-2.69 (m, 2H) 2.54 (br. s., 3 H) 2.25-2.38 (m, 1H) 2.23 (br. s., 3 H) 2.00-2.19 (m, 3 H) 1.34 (br. s., 3 H) 1.16 (br. s., 3 H) 1.14 (d, 3 H).

EJEMPLO 92

N-[6-[(7*R*)-8-acetil-7-(hidroximetil)octahidro-2*H*-pirazin[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E92)



A una solución de acetato de {(3*R*)-2-acetil-8-[5-[{2-[3,5-bis(trifluorometil)fenil]-2-metilpropanoil}(metil)amino]-4-(4-fluoro-2-metilfenil)-2-piridinil] octahidro-2*H*-pirazino[1,2-a]pirazin-3-il}metilo (D97, 27 mg, 0.0472 mmoles) en 2 ml de THF y 0.5 ml de agua se añadió NaOH 1 M (1 ml) y la solución resultante se agitó a temperatura ambiente durante 30 min. Se verificó por UPLC/MS, que mostró un pico para el producto esperado a 0.76 min. (m/z = 710 (M+1), 355 (M+2)/2). El compuesto objetivo se aisló por SCX,

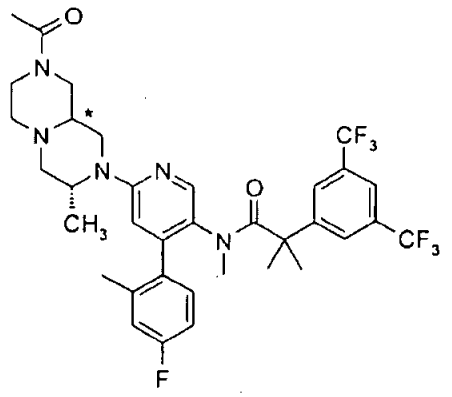
obteniendo 21 mg del compuesto del título.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.88 (s, 1H) 7.63-7.79 (m, 2H) 6.99-7.18 (m, 3 H) 6.76 (s, 1H) 4.84 (t, 1H) 4.13-4.42 (m, 3 H) 3.78-3.91 (m, 1H) 3.63-3.77 (m, 1H) 3.51-3.65 (m, 1H) 2.72-2.95 (m, 2H) 2.49 (s, 3 H) 2.08 (s, 3 H) 2.03 (s, 3 H) 1.90-2.67 (m, 6 H) 1.33 (s, 6 H)

Relación de diaestereoisómeros 1 y 2 no determinada.

EJEMPLO 93

_N_-[6-[(3_R_, 9a_R_ o 9a_S_)-8-acetil-3-metiloctahidro-2_H_-pirazino[1,2-_a_]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-_N_,2-dimetilpropanamida (E93 - Diaestereoisómero 1)



A una solución de (7_R_, 9a_R_ o 9a_S_)-2-acetil-7-metiloctahidro-2_H_-pirazin[1,2-_a_]pirazina (D100, 50 mg, 0.253 mmoles) en 1.1 ml de tolueno se añadió 2-[3,5-bis(trifluorometil)fenil]-_N_-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-_N_,2-dimetilpropanamida [WO 2005/002577] (112.6 mg, 0.211 mmoles), bis-tri-ter-butilfosfinopaladio (27 mg, 0.053 mmoles), cloruro de hexadeciltrimetilamonio (14 µl de una solución acuosa al 25%) y, por último,

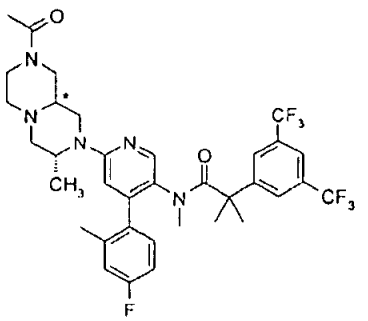
solución de hidróxido de sodio (25 µl de una solución acuosa al 50%). La solución se desgasificó mediante tres ciclos de congelamiento-bombeo-descongelamiento, después se agitó a 90°C durante 2.5 hr. Se verificó por CLAR/EM, que mostró un pico para el producto esperado a 2.07 min. (m/z = 694 (M+1)). La solución se diluyó con EtOAc, se extrajo con $NaHCO_3$ saturado y se secó (Na_2SO_4). El producto se aisló por cromatografía instantánea (EtOAc a EtOAc:MeOH 90:10), obteniendo 138 mg del compuesto del título.

O.A. CLAR: pico a 5.20 min, 97% de pureza (UV).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.03 (s, 1H) 7.98 (s, 1H) 7.75 (br. s., 2H) 7.16 (d, 1H) 7.10 (br. s., 2H) 6.76 (s, 1H) 4.16 (d, 1H) 3.82-3.95 (m, 1H) 3.61 (t, 1H) 3.48 (br. s., 1H) 3.14-3.26 (m, 1H) 2.95-3.10 (m, 2H) 2.64-2.82 (m, 1H) 2.50 (br. s., 3 H) 2.43-2.61 (m, 1H) 2.16-2.40 (m, 2H) 2.05-2.18 (m, 4 H) 1.97 (s, 3 H) 1.48 (br. s., 3 H) 1.34 (br. s., 3 H) 1.15 (d, 3 H).

EJEMPLO 94

N-[6-[(3*R*, 9a*S* o 9a*R*)-8-acetil-3-metiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida (E94 - Diaestereoisómero 2)



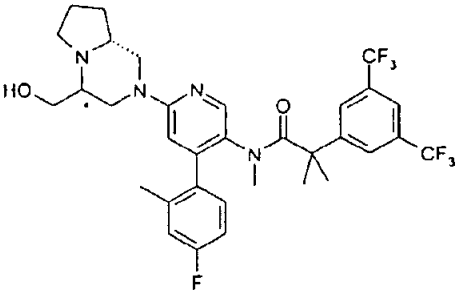
A una solución de (7*R*, 9a*R* o 9a*S*)-2-acetil-7-metiloctahidro-2*H*-pirazin[1,2-*a*]pirazina y (7*R*, 9a*S* o 9a*R*)-2-acetil-7-metiloctahidro-2*H*-pirazin[1,2-*a*]pirazina (D100 más D101, 75 mg, 0.38 mmoles) en 1.1 ml de tolueno se añadió 2-[3,5-bis(thfluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (169 mg, 0.317 mmoles), bis-tri-ter-butilfosfinopaladio (40.5 mg, 0.079 mmoles), cloruro de hexadeciltrimetilamonio (20 µl de una solución acuosa al 25%) y, por último, solución de hidróxido de sodio (38 µl de una solución acuosa al 50%). La solución se desgasificó mediante tres ciclos de congelamiento-bombeo-descongelamiento, se agitó a 90°C durante 6.5 hr. Se verificó por CLAR/EM, que mostró picos para los productos esperados a 1.98 y 2.28 min. (m/z = 694 (M+1)). La solución se diluyó con EtOAc, se extrajo con $NaHCO_3$ saturado y se secó (Na_2SO_4). El producto se aisló por cromatografía instantánea (diclorometano a diclorometano:MeOH 90:10). Se obtuvieron 32.4 mg del compuesto del título.

O.A. CLAR: pico a 5.25 min, 95% de pureza (UV).

^{1}H RMN (500 MHz; DMSO-d_6) δ ppm 8.02 (s, 1H) 7.88 (s, 1H) 7.74 (br. s., 2H) 7.15 (d, 1H) 7.10 (br. s., 2H) 6.61 (br. s., 1H) 4.52 (br. s., 1H) 4.34 (t, 1H) 4.08 (br. s., 1H) 3.81 (dd, 1H) 3.28-3.35 (m, 1H) 2.85 (t, 1H) 2.59-2.78 (m, 3 H) 2.50 (br. s., 3 H) 2.10-2.38 (m, 2H) 2.10 (br. s., 3 H) 1.99 (s, 3 H) 1.77-1.96 (m, 1H) 1.48 (br. s., 3 H) 1.33 (br. s., 3 H) 1.16 (d, 3 H).

EJEMPLO 95 y 96

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(4*S* o 4*R*, 8a*R*)-4-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E95 - Diaestereoisómero 1) 2-[3,5-bis(trifluorometil) fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(4*R* o 4*S*, 8aR)-4-(hidroximetil) hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E96 - Diaestereoisómero 2)



A una solución de (8a*R*)-octahidropirrolo[1,2-*a*]pirazin-4-ilmetanol (D112, 73 mg, 0.468 mmoles) y 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (124 mg, 0.234 mmoles) en DMSO (0.75 ml) se añadió K_2CO_3 (96 mg, 0.702 mmoles) y la mezcla de reacción se agitó durante 36 hr a 120/150°C.

Los dos diaestereoisómeros se aislaron después de purificación por SCX y por cromatografía (sílice, CH_2Cl_2:MeOH 98:2).

E95- Diaestereoisómero 1 (40 mg)

EM: m/z= 653 (M+1) y 327 ($^{M}/_{2}$+1)

CLAR: pico a t=5.22 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.88 (s, 1H)

7.73 (br. s., 2H) 7.14 (d, 1H) 7.10 (br. s., 2H) 6.63 (br. s., 1H) 4.62 (s, 1H) 4.32-4.44 (m, 2H) 3.57-3.66 (m, 1H) 3.30-3.36 (m, 2H) 3.11-3.20 (m, 1H) 2.48 (s, 3 H) 2.41-2.58 (m, 2H) 2.24 (br. s., 1H) 2.15 (s, 3 H) 2.10 (br. s., 1H) 1.73-1.83 (m, 1H) 1.60-1.70 (m, 4 H) 1.33 (s, 3 H) 1.10-1.54 (m, 2H)

E96- Diaestereoisómero 2 (33 mg)

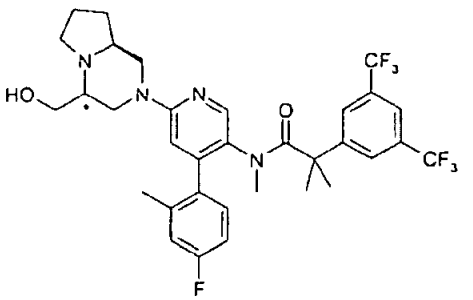
EM: m/z= 653 (M+1) y 327 ($^{M}/_{2}$+1)

CLAR: pico a t=5.152 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.84 (s, 1H) 7.73 (br. s., 2H) 7.14 (d, 1H) 7.10 (br. s., 2H) 6.51 (s, 1H) 4.48-4.57 (m, 1H) 3.88-3.98 (m, 1H) 3.48-3.61 (m, 3 H) 3.33-3.37 (m, 1H) 3.06-3.18 (m, 1H) 2.81-2.94 (m, 3 H) 2.68-2.76 (m, 1H) 2.49 (s, 3 H) 2.11 (s, 3 H) 1.79-1.90 (m, 1H) 1.70-1.79 (m, 1H) 1.56-1.69 (m, 1H) 1.33 (s, 6 H) 1.23-1.41 (m, 1H).

EJEMPLO 97 y 98

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(4*S* o 4*R*, 8a*S*)-4-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E97 - Diaestereoisómero 1) 2-[3,5-bis (trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(4*R* o 4*S*, 8a*S*)-4-(hidroximetil)hexahidropirrolo[1,2-*a*]pirazin-2(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E98 - Diaestereoisómero 2)



A 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (375 mg, 0.705 mmoles) y K_2CO_3 (389 mg) se añadió una solución de (8a*S*)-octahidropirrolo [1,2-*a*]pirazin-4-ilmetanol (D117, 220 mg, 1.41 mmoles) en DMSO (2.3 ml) y la mezcla de reacción se agitó durante 30 hr a 150°C.

Los dos diaestereoisómeros se aislaron después de purificación por SCX y además por cromatografía (cartucho de sílice, CH_2Cl_2:MeOH 98:2).

E97- Diaestereoisómero 1 (150 mg):

EM: m/z= 653 (M+1) y 327 ($^M/_2$+1)

CLAR: pico a t=5.18 min

UPLC/MS: m/z= 653 (M+1) y 327 ($^M/_2$+1) a t=0.70 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.88 (s, 1H) 7.73 (br. s., 2H) 7.14 (d, 1H) 7.10 (br. s., 2H) 6.63 (br. s., 1H) 4.62 (s, 1H) 4.32-4.44 (m, 2H) 3.57-3.66 (m, 1H) 3.30-3.36 (m, 2H) 3.11-3.20 (m, 1H) 2.48 (s, 3 H) 2.41-2.58 (m, 2H) 2.24 (br. s., 1H) 2.15 (s, 3 H) 2.10 (br. s., 1H) 1.73-1.83 (m, 1H) 1.60-1.70 (m, 4 H) 1.33 (s, 3 H) 1.10-1.54 (m, 2H)

E98- Diaestereoisómero 2 (75 mg):

EM: m/z= 653 (M+1) y 327 ($^M/_2$+1)

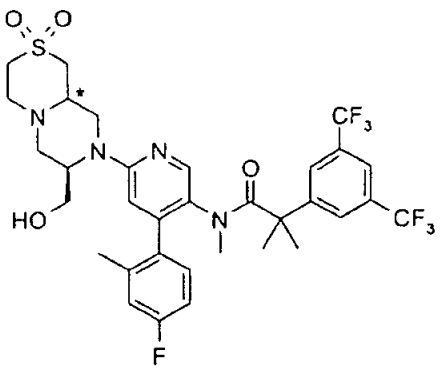
CLAR: pico a t=5.15 min

UPLC/MS: m/z= 653 (M+1) y 327 ($^M/_2$+1) a t=0.72 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.84 (s, 1H) 7.73 (br. s., 2H) 7.14 (d, 1H) 7.10 (br. s., 2H) 6.51 (s, 1H) 4.48-4.57 (m, 1H) 3.88-3.98 (m, 1H) 3.48-3.61 (m, 3 H) 3.33-3.37 (m, 1H) 3.06-3.18 (m, 1H) 2.81-2.94 (m, 3 H) 2.68-2.76 (m, 1H) 2.49 (s, 3 H) 2.11 (s, 3 H) 1.79-1.90 (m, 1H) 1.70-1.79 (m, 1H) 1.56-1.69 (m, 1H) 1.33 (s, 6 H) 1.23-1.41 (m, 1H).

EJEMPLO 99

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[{7*R*, 9a*R* o 9a*S*)-7-(hidroximetil)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E99- Diaestereoisómero 1)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*R*, 9a*R* o 9a*S*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2,2-dioxidohexahidropirazino [2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D124, 201 mg, 0.24 mmoles) en metanol (8 ml), enfriada a 0°C, se añadió HCl 12 N gota a gota (0.47 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 hr, después se purificó por cartucho de SCX. Las fracciones eluidas con amoniaco metanólico 2M se combinaron y se evaporaron a sequedad para dar el compuesto del título como un sólido blanco (155 mg, rendimiento =90%).

CLAR: pico a t=5.65 min

CLAR/EM: m/z= 717 (M+1) a t=2.88 min

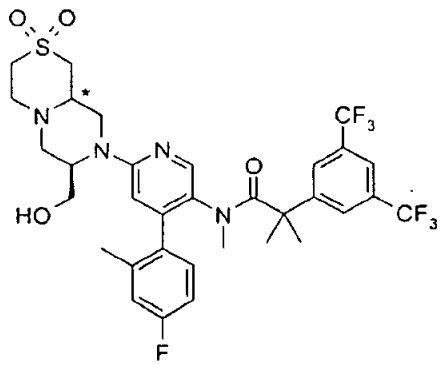
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.95-8.10 (m, 1H) 7.80-7.93 (m, 1H) 7.59-7.81 (m, 2H) 6.86-7.24 (m, 3 H) 6.49-6.76 (m, 1H) 4.63-4.79 (m,

630

1H) 3.94-4.42 (m, 2H) 3.55-3.84 (m, 1H) 2.86-3.52 (m, 7 H) 1.00-2.83 (m, 16 H).

EJEMPLO 100

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*R*, 9a*S* o 9a*R*)-7-(hidroximetil)-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E100- Diaestereoisómero 2)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*R*, 9a*S* o 9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2,2-dioxidohexahidropirazino [2,1-*c*][1,4]tiazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (D125, 127.4 mg, 0.153 mmoles) en metanol (5 ml), enfriada a 0°C, se añadió gota a gota HCl 12 N (0.3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 hr,después se purificó por cartucho de SCX. Las fracciones eluidas con amoniaco metanólico 2M se combinaron y se evaporaron a sequedad para dar el compuesto del título como un sólido blanco (104 mg, rendimiento =95%).

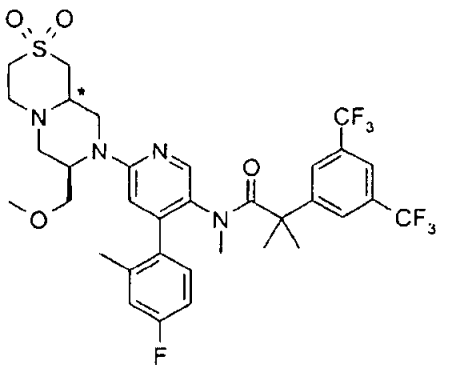
CLAR: pico a t=5.54 min

CLAR/EM: m/z= 717 (M+1) a t=2.91 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.85 (s, 1H) 7.63-7.81 (m, 2H) 7.16 (d, 1H) 7.03-7.17 (m, 2H) 6.67 (s, 1H) 4.71 (t, 1H) 4.19-4.36 (m, 1H) 4.02-4.19 (m, 1H) 3.65-3.80 (m, 1H) 3.36-3.53 (m, 1H) 3.15-3.36 (m, 4 H) 3.10 (d, 1H) 2.86-3.01 (m, 1H) 2.72-2.84 (m, 1H) 2.65 (d, 1H) 1.10-2.56 (m, 14 H).

EJEMPLO 101

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*R*, 9a*R* o 9a*S*)-7-[(metiloxi)metil]-2,2-dioxidohexahidropirazino[2,1-*c*][1,4]tiazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E101- Diaestereoisómero 1)



A una solución de 2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[{7*R*, 9a*R* o 9a*S*)-7-(hidroximetil)-2,2-dioxidohexahidropirazino [2,1-*c*][1,4]tiazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E99, 15 mg, 0.021 mmoles) en THF (1 ml) se añadió, bajo N_2, a t.a., NaH al 60% (1 mg, 0.023 mmoles) y la mezcla de reacción se agitó durante 30 min. Después, se añadió MeI (2 µl, 0.021 mmoles) y la mezcla de reacción se agitó durante 6 hr.

Durante este tiempo de reacción, cantidades adicionales de NaH (2 mg, 0.046 mmoles) y MeI (4 µl, 0.042 mmoles) se añadieron en porciones.

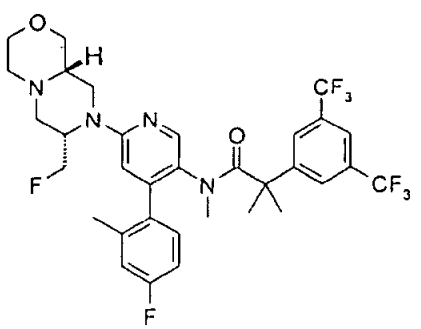
Se añadió agua a la mezcla de reacción y la fase acuosa se extrajo con EtOAc (3X). Las fases orgánicas combinadas se secaron y se evaporaron a sequedad. El crudo se purificó dos veces por cromatografía (sílice, CH_2Cl_2:MeOH 1:0 a 8:2 la 1a. vez y CH_2Cl_2:MeOH 1:0 a 9:1 la 2a. vez) para dar el compuesto del título (12.4 mg, rendimiento =81 %)

EM: m/z= 731 (M+1); 753 (M+Na); 366 ($^{M}/_{2}$+1)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.87 (s, 1H) 7.63-7.81 (m, 2H) 7.15 (d, 1H) 7.02-7.19 (m, 2H) 6.66 (s, 1H) 4.44-4.77 (m, 1H) 3.99-4.27 (m, 1H) 3.67 (t, 1H) 3.37-3.50 (m, 1H) 3.23 (s, 3 H) 2.91-3.39 (m, 7 H) 2.68-2.85 (m, 1H) 2.51 (s, 3 H) 2.40-2.66 (m, 1H) 2.11-2.29 (m, 1H) 2.11 (s, 3 H) 1.49 (s, 3 H) 1.34 (s, 3 H).

EJEMPLO 102

2-[3,5-bis(trifluorometil)fenil]-*N*-[6-[(7*S*, 9a*S*)-7-(fluorometil) hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida (E102)



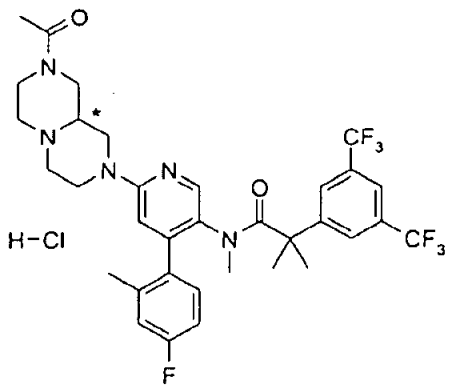
A una solución de (7*S*,9a*S*)-7-(fluorometil)octahidropirazino[2,1-*c*][1,4]oxazina (D129, 14.9 mg, 0.086 mmoles) en tolueno (1 ml) se añadió bajo N_2, a t.a., 2-cloropiridina (35 mg, 0.066 mmoles) y después cloruro de hexadeciltrimetilamonio (4 µl de una solución acuosa al 25%), bis-tri-ter-butilfosfinopaladio (7 mg), y solución de hidróxido de sodio (8 µl de una solución acuosa al 50%). La mezcla de reacción se desgasificó por ciclos de congelamiento-bombeo-descongelamiento y después se agitó a 90°C durante 1 hr. EtOAc y $NaHCO_3$ se añadieron a la mezcla de reacción, las dos fases se separaron y la fase acuosa se extrajo con EtOAc (3X). Las fases orgánicas combinadas se secaron (Na_2SO_4) y se evaporaron a sequedad. El crudo se purificó por cromatografía (sílice, ciclohexano:EtOAc 7:3 a 0:1) para dar el compuesto del título como una espuma pardusca (30 mg, rendimiento = 68%).

UPLC/MS: m/z= 671 (M+1) a t=0.93 min

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.01 (s, 1H) 7.88 (s, 1H) 7.60-7.80 (m, 2H) 6.99-7.23 (m, 3 H) 6.69 (s, 1H) 4.66-4.89 (m, 1H) 4.56-4.73 (m, 1H) 3.96-4.09 (m, 1H) 3.67-3.79 (m, 2H) 3.54 (t, 1H) 3.14 (t, 1H) 2.89 (d, 1H) 2.49-2.69 (m, 1H) 2.50 (s, 3 H) 2.04-2.38 (m, 2H) 2.09 (s, 3 H) 1.53-1.74 (m, 1H) 1.34 (s, 6 H) 1.11-1.46 (m, 1H) 1.03-1.43 (m, 1H).

EJEMPLO 103

HCl: Clorhidrato de *N*-[6-[(9a*R* o 9a*S*)-8-acetiloctahidro-2*H*-pirazin[1,2-*a*]pirazin-2-il]-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil) fenil]-*N*,2-dimetilpropanamida (E103 - Enantiómero 2)

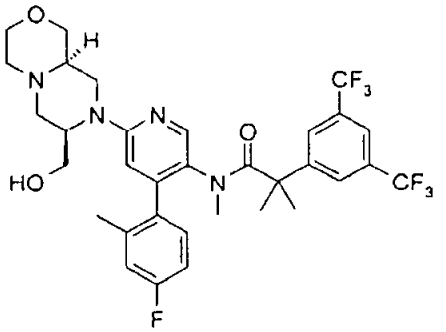


A una solución de *N*-[6-(8-acetiloctahidro-2*H*-pirazino[1,2-*a*]pirazin-2-il)-4-(4-fluoro-2-metilfenil)-3-piridinil]-2-[3,5-bis(trifluorometil)fenil]-*N*,2-dimetilpropanamida, enantiómero 2 (E72, 19 mg, muestra de una preparación diferente que tiene características analíticas comparables a la reportada) en éter dietílico a 0°C se añadieron 33.5 µl de una solución HCl 1M en éter dietílico. La solución se agitó durante 10 minutos y el solvente se removió bajo una corriente de nitrógeno. El residuo se trituró con éter dietílico y pentano y se recogió por filtración. Se obtuvieron 20 mg del compuesto objetivo.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 10.27-10.61 (m, 1H) 8.04 (s, 1H) 7.94 (s, 1H) 7.62-7.81 (m, 2H) 7.17 (d, 1H) 7.04-7.16 (m, 2H) 6.86 (s, 1H) 4.44-4.76 (m, 3 H) 3.97-4.26 (m, 1H) 2.73-3.91 (m, 7 H) 2.48 (s, 3 H) 2.09-2.54 (m, 2H) 2.11 (s, 3 H) 2.05 (s, 3 H) 1.49 (s, 3 H) 1.38 (s, 3 H).

EJEMPLO 104

2-[3,5-bis(trifluorometil)fenil]-*N*-{4-(4-fluoro-2-metilfenil)-6-[(7*R*, 9a*R*)-7-(hidroximetil)hexahidropirazino[2,1-*c*][1,4]oxazin-8(1*H*)-il]-3-piridinil}-*N*,2-dimetilpropanamida (E104)



(7*R*, 9a*R*)-7-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)octahidropirazino[2,1-*c*][1,4]oxazina (D132, 85 mg, 0.297 mmoles) se disolvió en 1 ml de tolueno agitando a temperatura ambiente. Se añadió 1 ml adicional de tolueno para obtener disolución completa. Se añadió una muestra de 2-[3,5-bis(trifluorometil)fenil]-*N*-[6-cloro-4-(4-fluoro-2-metilfenil)-3-piridinil]-*N*,2-dimetilpropanamida [WO 2005/002577] (143 mg, 0.268 mmoles), seguido por una solución de 2-diciclohexilfosfino-2'-(*N*,*N*-dimetilamino)bifenilo (ligando) (13 mg, 0.033 mmoles) y $Pd(dba)_2$ (8 mg, 0.014 mmoles) en 1 ml de tolueno. Se añadió *ter*-butóxido de potasio (39 mg, 0.406 mmoles) y el recipiente de reacción se cerró, se evacuó y se volvió a llenar con argón. La mezcla se hizo reaccionar bajo irradiación de microondas a 140°C durante 15 min y después durante 30 min adicionales. La mezcla se diluyó con 30 ml de EtOAc y se extrajo con $NaHCO_3$ saturado, se secó (Na_2SO_4) y el solvente se removió. El

producto se purificó por cromatografía instantánea: sílice, ciclohexano:EtOAc 100:0 a 80:20. Se obtuvo una muestra parcialmente purificada: analizada por UPLC/MS (pureza: 24% por rastreo con UV, 58% por rastreo con EM), se usó directamente en el paso de desprotección.

UPLC/MS: pico a 1.21 min, m/z= 783 (M+1), 392 (M+2/2).

El intermediario (55 mg) se disolvió en 2 ml de metanol y se añadió 0.1 ml de HCl concentrado. La solución se agitó a temperatura ambiente durante 1 hr. Se cargó sobre un cartucho de SCX, se lavó con MeOH, y el producto se eluyó con amoniaco 1M en MeOH. El análisis de UPLC/MS mostró el pico de producto esperado a 0.75 min (m/z= 669, M+1; 335, (M+2)/2). Este se purificó adicionalmente por cromatografía instantánea (sílice, ciclohexano:EtOAc 50:50 a 0:100). Se obtuvieron 12 mg.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.02 (s, 1H) 7.84 (s, 1H) 7.74 (br. s., 2H) 7.15 (d, 1H) 7.10 (br. s., 2H) 6.60 (s, 1H) 4.65-4.75 (m, 1H) 4.22 (br. s., 1H) 4.08 (br. s., 1H) 3.68-3.80 (m, 3 H) 3.53 (t, 1H) 3.34-3.43 (m, 1H) 3.14 (t, 1H) 3.01 (d, 1H) 2.63 (d, 1H) 2.48 (s, 3 H) 2.17 (s, 3 H) 2.00-2.29 (m, 4 H) 1.46 (s, 3 H) 1.34 (s, 3 H).

Datos biológicos

Los compuestos de la invención se pueden probar para actividad biológica *in vitro* de conformidad con las siguientes pruebas:

Medición de afinidad de unión de NK

La afinidad de unión de NK de los compuestos en la invención se determinó usando la siguiente prueba de proximidad de escintilación (SPA) (véase H. M. Sarau et al, J. Pharmacol. Experimental Therapeutics 1997, 281.(3), 1303-1311; H. M. Sarau et al, J. Pharmacol. Experimental Therapeutics 2000, 295(1), 373-381; G. A. M. Giardina et al J.Med.Chem 1999, 42, 1053-1065). ^{125}I-Sustancia P, ^{125}I-NKA y ^{125}I-[MePhe7]-NKB se usaron en SPA de unión de receptor NK1, NK2 y NK3, respectivamente. Esferas de poliestireno Leadseeker WGA-SPA (Amersham Biosciences) se mezclaron con membrana plasmática preparada a partir de líneas celulares de CHO que expresaban NK1, NK2 o NK3 en una relación de esfera/membrana de 20:1 (p/p) en un regulador de pH de prueba (75 mM Tris pH 7.8, 75mM NaCl, 4 mM $MnCl_2$, 1 mM EDTA, 0.05% Chaps, 1 mM PMSF). La mezcla se puso sobre hielo durante 20 minutos para permitir la formación de complejo de membrana/esfera antes de que BSA se añadiera a una concentración final de 1%. Después de otros 20 minutos de incubación sobre hielo, el complejo de esfera/membrana se lavó dos veces y se suspendió en un regulador de pH de prueba. Ligandos ^{125}I-marcados se añadieron después al complejo de esfera/membrana. 10 µl de la mezcla resultante se suministraron después en cada pozo de una placa de 384 pozos Greiner de volumen bajo con 100 nl de compuesto pre-suministrado en 100% de DMSO. Las placas después se sellaron y se hicieron girar por pulsos a 1100 rpm. Después de 2-3 horas de incubación a temperatura ambiente con agitación, las placas se hicieron girar

durante 2 min a 1100 rpm y se midieron en un formador de imágenes Viewlux (PerkinElmer) durante 5 minutos con un filtro de 618-nm. La inhibición de unión de ligando radioactivo a su receptor respectivo se midió por la reducción de signal. pK_i se calculó usando K_d de cada ligando radioactivo determinado en un experimento separado.

Medición de afinidad funcional de NK

Prueba de movilización de calcio en (FLIPR): receptores de NK expresados por Bacman

Los compuestos de la invención se caracterizaron además en una prueba funcional con el uso de tecnología FLIPR para la determinación de su efecto para inhibir la liberación de calcio intracelular inducida por interacción de receptores de NK con sus ligandos en perspectiva. Células U2OS humanas transitoriamente transducidas con virus BacMan recombinante que expresaba receptores de NK1, NK2 y NK3 se usaron en los estudios (véase J. P. Condreay et al, Proc. Natl. Acad. Sci. USA 1999, 96(1): 127-132). En breve, las células U2OS se cosecharon de matraces con cultivo de tejido, se re-suspendieron a una densidad de células de 200-300K/ml y se mezclaron con virus de BacMan recombinante que portaba el gen NKR en una relación de virus/célula de 1% (v/v). 10K-15K células/pozo se sembraron después en placa de 384 pozos Greiner bio-one en un medio de cultivo (DMEM con 10% de FBS), se incubaron durante la noche en CO_2 a 37°C. Después de aspirar el medio, las células se cargaron 18-24 hr más tarde con

colorante de calcio 3 como indicador de calcio citoplásmico (Molecular Devices Co.) en 30ul/pozo de regulador de pH (sales balanceadas de Hank con 20 mM Hepes) y se incubaron en CO_2 a 37°C durante 60 minutos. 10 ul/pozo de regulador de pH de prueba (sales balanceadas de Hank con 20 mM de Hepes) que contenían diferentes concentraciones de compuestos se añadieron a las células durante 30 minutos de incubación a 37°C. Finalmente, 10 ul/pozo de ligandos NKR en regulador de pH de prueba que contenía 0.1% de BSA se añadió a las células y la señal de fluorescencia se leyó en un sistema FLIPR. Los péptidos de sustancia P, NKA y NKB se usaron como los ligandos para receptor de NK1, NK2 y NK3, respectivamente. Los valores de CI50 de cada compuesto fueron determinados por una curva de inhibición de dilución de 3 veces de 11 puntos. La potencia de cada antagonista (fpK_i) se calculó a partir de pIC50 por la ecuación de Cheng-Prusoff mediante el uso de EC50 de ligando determinada en un experimento separado.

Medición de afinidad funcional de NK3

Prueba de movilización de calcio en (FLIPR): receptores de NK establemente expresados

Receptores de neuroquinina 3 (NK_3) clonados humanos establemente expresados en células de riñón embrionario humano (HEK 293) se mantuvieron en un medio esencial mínimo (MEM, 31095-029 Invitrogen Life Technologies, Paisley, UK) complementado con 5% de suero de bovino fetal, 1% de L-glutamina y 400-500 µg de geneticina y fueron sub-cultivados

con el uso de Accutase (PAA Labs, Austria). Las células se mantuvieron a 37°C, 5% de CO_2/O_2 en una incubadora humidificada. Los cambios en Ca^{2+} intracelular se determinaron con el uso de un lector de placa de formación de imagen por fluorescencia (FLIPR) (Molecular Devices, Sunnyvale CA, E.U.A.) por un método similar I descrito por Jerman et al, (2001). Células HEK 293 que expresaban establemente el receptor de NK_3 humano se sembraron en placas de 96 pozos revestidos con poli-d-lisina de base clara con pared negra (Costar, R.U.) a una densidad de 25,000 células por pozo incubado durante la noche. Las células se incubaron (37°C durante 60 min) con calcio más reactivo (Molecular Devices) en regulador de pH Tyrodes (NaCl, 145 mM; KCl, 2.5 mM; HEPES, 10 mM; glucosa, 10 mM; $MgCl_2$, 1.2 mM; $CaCl_2$, 1.5 mM) que contenía probenecid (2.5 mM), antes de la incubación (30 min a 37°C) con ya sea con regulador de pH o antagonista (50 µl). Las placas se colocaron después sobre el FLIPR y 50 µl de NKB se añadieron (10 pM - 1 µM de concentración final) y los cambios en fluorescencia se monitorearon. Los cambios pico en fluorescencia ocurrieron dentro de los primeros 5 segundos y se reportaron después de sustracción de línea basal. Las curvas de concentración-respuesta se analizaron con el uso de una ecuación logística de 4 parámetros (GraphPad Prism, GraphPad Software Inc.) para obtener valores de PEC_{50} (-log EC_{50}), los valores de pA_2 se obtuvieron por análisis de Schild. Los datos son de la media ± media del error estándar de tres experimentos separados.

Prueba de acumulación de fosfatos de inositol [^{3}H]

La acumulación de fosfatos de inositol [^{3}H] se midió con el uso de la metodología de Brandish et al., (2003). En breve, células de osteosarcoma humanas (células U-2OS) se cultivaron en medio de Tagle modificado por Dulbecco (DMEM) con 10% de suero de ternera fetal. Las células se mantuvieron a 5% de CO_2/O_2 en una incubadora humidificada a 37°C. Todos los reactivos de cultivo de células se obtuvieron de Invitrogen, Paisley, R.U. Las células U-2OS se hicieron crecer a confluencia, se cosecharon y se suspendieron en un medio de crecimiento a una densidad de 250000 células por ml. Virus bacman de NK_3 humano se añadieron a una concentración de 50 unidades formadoras de placa por célula. 25000 células por pozo se sembraron en placas de 96 pozos de base clara con pared negra (Corning Costar, R.U.) incubados durante la noche. Después de la aspiración de medio de crecimiento, las células se lavaron con 2 x 200 µl de medio de prueba libre de inositol (IF), 3% de albúmina de suero de bovino, 2 µM de L-glutamina. Las células se incubaron durante 16 hr con DMEM libre de inositol en presencia de [^{3}H]-mio-inositol 1 µCi por pozo (Amersham R.U.).

El medio de crecimiento después se aspiró y las células se lavaron con 2 x 200 µl de IF DMEM. Las células se pre-incubaron (30 min, 37°C) en ausencia o presencia de compuestos de prueba antes de la adición de varias concentraciones de NKB (0.1 nM - 10 mM) en presencia de LiCl (5 mM). Después de 30 min de incubación con el agonista, la prueba se terminó por aspiración del medio de prueba y la adición de 200 ul de ácido fórmico 0.1

M a las células. Después de una hora de incubación, alícuotas de 20 ul se mezclaron con 80 ul de esferas de silicato de itrio en placas pico blancas sólidas (PerkinElmer). Las placas se agitaron suavemente durante 1 hr antes de permitir que la mezcla de esferas se sedimentara durante 2 hr. Las placas se contaron en TopCount (PerkinElmer). Los datos se presentan como un porcentaje de la respuesta de NKB máxima. Las curvas de concentración-respuesta se analizaron con el uso de una ecuación logística de 4 parámetros (GraphPad Prism, GraphPad Software Inc.). Los valores de pA_2 se obtuvieron por análisis de Schild. Los datos son de la media ± media del error estándar de tres experimentos.

Resultados

Los compuestos de los ejemplos E1 a E33 se probaron en la prueba de afinidad de unión de NK1 y presentaron afinidad de unión > 8.0 pK_i.

Los compuestos de los ejemplos E34-E40 y E72 presentaron afinidad de unión en la prueba de afinidad de unión de NK1 > 8.5 pK_i.

Los compuestos de los ejemplos E41-E71 y E73-E104 presentaron afinidad de unión en la prueba de afinidad de unión de NK1 > 8.0 pK_i.

Los compuestos de los ejemplos E1 a E33 también se probaron en la prueba de afinidad de unión de NK3 y presentaron afinidad de unión > 5.5 pK_i.

Los compuestos de los ejemplos E34-E40 y E72 presentaron

afinidad de unión en la prueba de afinidad de unión de NK3 ≥ 8.0 pK_i.

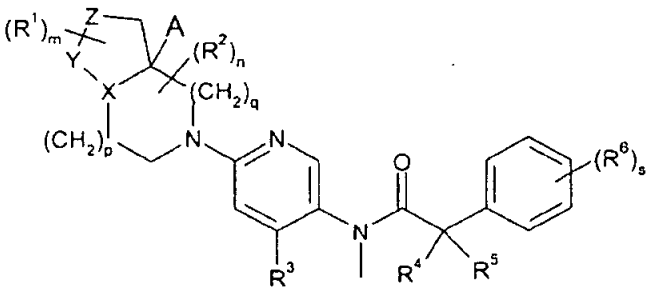
Los compuestos de los ejemplos E41-E71 y E73-E104 presentaron afinidad de unión en la prueba de afinidad de unión de NK3 > 5.0 pK_i.

5

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo:



(I)

en donde: X representa un átomo de nitrógeno; Y representa $-C(H_2)-$, $(-C(H_2)-)_2$. $-S(O_2)-$ o $-C(=O)-$; Z representa $-C(H_2)-$, $-S(O_2)-$, $-N(R^Z)-$, o un átomo de oxígeno o azufre; A representa hidrógeno o $-CH_2OH$; R^z representa hidrógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, $-COR^7$ o $-SO_2R^7$; R^1 representa halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, =O, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6}, hidroxilo o $-CH_2OH$; m representa un entero de 0 a 3; R^2 representa halógeno, =O, alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), $-COOR^7$, $-CONR^7R^8$, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6} o alquilo de C_{1-6}-O-alquilo de C_{1-6}; n representa un entero de 0 a 3; p y q independientemente representan un entero de 0 a 2; R^3 representa un grupo -arilo, -heteroarilo, -heterociclilo, -aril-

arilo, -aril-heteroarilo, -aril-heterociclilo, -heteroaril-arilo, -heteroaril-heteroarilo, -heteroaril-heterociclilo, -heterociclil-arilo, -heterociclil-heteroarilo o -heterociclil-heterociclilo, todos los cuales pueden ser opcionalmente sustituidos por uno o más (v.gr., 1, 2 ó 3) halógeno, grupos alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, hidroxilo, halogenoalquilo de C_{1-6}, halogenoalcoxi de C_{1-6}, ciano, -S-alquilo de C_{1-6}, -SO-alquilo de C_{1-6}, -SO_2-alquilo de C_{1-6}, -COR^7, -$CONR^7R^8$, -NR^7R^8, NR^7CO-alquilo de C_{1-6}, NR^7SO_2-alquilo de C_{1-6}, alquilo de C_{1-6}-NR^7R^8, -$OCONR^7R^8$, -$NR^7CO_2R^8$ o -$SO_2NR^7R^8$; R^4 y R^5 independientemente representa alquilo de C_{1-6}, o R^4 y R^5 junto con el átomo de carbono al cual están unidos juntos pueden formar un grupo cicloalquilo de C_{3-8}; R^6 representa halógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6}; s representa un entero de 0 a 4; R^7 y R^8 independientemente representa hidrógeno, alquilo de C_{1-6} o cicloalquilo de C_{3-8}; o solvatos de los mismos.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-.

3.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa un átomo de oxígeno.

4.- El compuesto de conformidad con la reivindicación 1,

caracterizado además porque p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -$S(O_2)$- y Z representa -$C(H_2)$-.

5.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa -C(=O)- y Z representa -$C(H_2)$-.

6.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p representa 1, q representa 2, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-.

7.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p representa 2, q representa 1, X representa un átomo de nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-.

8.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa -$S(O_2)$-.

9.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa nitrógeno, Y representa $(-C(H_2)-)_2$ y Z representa -$N(R^Z)$-.

10.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p representa zero, q representa 1, X representa nitrógeno, Y representa -$C(H_2)$- y Z representa -$C(H_2)$-.

11.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10, caracterizado además porque m representa 0 ó 1.

12.- El compuesto de conformidad con cualquiera de las

reivindicaciones 1 a 11, caracterizado además porque n representa 0 ó 1.

13.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 12, caracterizado además porque R^1 representa =0, hidroxilo, $-CH_2OH$.

14.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 13, caracterizado además porque R^2 representa =O, alquilo de C_{1-6}, alquilo de C_{1-6}-O- alquilo de C_{1-6}, halogenoalquilo de C_{1-6} o alquilo de C_{1-6} sustituido por un grupo hidroxilo.

15.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 14, caracterizado además porque A representa hidrógeno o - CH_2OH.

16.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 15, caracterizado además porque R^7 representa alquilo de C_{1-6}.

17.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 16, caracterizado además porque Z representa $-N(R^Z)-$ y R^z representa hidrógeno, alquilo de C_{1-6}, $-COR^7$ o $-SO_2R^7$.

18.- El compuesto de conformidad con la reivindicación 17, caracterizado además porque R^7 representa alquilo de C_{1-6}.

19.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, caracterizado además porque R^3 representa -arilo monosustituido por un halógeno o grupo alquilo de C_{1-6}, -arilo disustituido por un halógeno y grupo alquilo de C_{1-6}, -arilo monosustituido por alquilo de C_{1-6}

sustituido por uno o más grupos hidroxilo, -arilo disustituido por un halógeno, -heteroarilo monosustituido por alquilo de C_{1-6} o -heteroarilo disustituido por un halógeno y un grupo alquilo de C_{1-6}.

20.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 19, caracterizado además porque R^4 y R^5 ambos representan alquilo de C_{1-6} o R^4 y R^5 junto con el átomo de carbono al cual están unidos forman un grupo cicloalquilo de C_{3-8}.

21.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 20, caracterizado además porque s representa 2 y ambos grupos R^6 son halogenoalquilo de C_{1-6}.

22.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa un átomo de oxigeno, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo, R^3 representa -arilo disustituido por un halógeno y grupo alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6} y s representa 2 en donde ambos grupos R^6 son halogenoalquilo de C_{1-6}.

23.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa un átomo de nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $-S(O_2)-$, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo, R^3 representa -arilo disustituido por un halógeno y grupo alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6} y s representa 2 en donde ambos

grupos R^6 son halogenoalquilo de C_{1-6}.

24.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, X representa nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $-N(R^Z)-$, n representa 1, R^2 representa alquilo de C_{1-6} sustituido por un grupo hidroxilo, R^3 representa -arilo disustituido por un halógeno y grupo alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6} y s representa 2 en donde ambos grupos R^6 son halogenoalquilo de C_{1-6}.

25.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque p y q ambos representan 1, n y m ambos representan 0, A representa hidrógeno, X representa nitrógeno, Y representa $(-C(H_2)-)_2$, Z representa $-N(R^Z)-$, R^3 representa -arilo sustituido por un halógeno y grupo alquilo de C_{1-6}, R^4 y R^5 ambos representan alquilo de C_{1-6}, s representa 2 en donde ambos R^6 grupos son halogenoalquilo de C_{1-6} y R^z representa $-COR_7$, en donde R_7 es alquilo de C_{1-6}.

26.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es un compuesto de la fórmula E1-E104 o una sal farmacéuticamente aceptable del mismo.

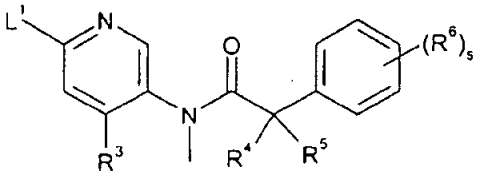
27.- El compuesto de conformidad con la reivindicación 1, seleccionado del grupo que consiste de: 2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S,9aS)-7-(hidroximetil)hexahidropirazino[2,1-c][1,4]oxazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida, 2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S,9aR)-7-

(hidroximetil)hexahidropirazino[2,1-c][1,4]oxazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida, 2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S)-7-(hidroximetil)-2,2-dioxidohexahidropirazino[2,1-c][1,4]tiazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida, N-[6-[(3S)-8-acetil-3-(hidroximetilo)octahidro-2H-pirazino[1,2-a]pirazin-2-il]-4-(4-fluoro-2-metilfenilo)-3-piridinil]-2-[3,5-bis(trifluorometilo)fenil]-N,2-dimetilpropanamida, o una sal farmacéuticamente aceptable de los mismos.

28.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es: 2-[3,5-bis(trifluorometilo)fenil]-N-{4-(4-fluoro-2-metilfenilo)-6-[(7S,9aR)-7-(hidroximetil)hexahidropirazino[2,1-c][1,4]oxazin-8(1H)-il]-3-piridinil}-N,2-dimetilpropanamida o una sal farmacéuticamente aceptable del mismo.

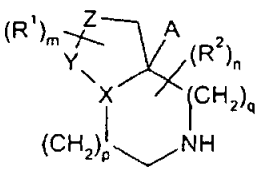
29.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es: N-[6-[(9aS o 9aR)-8-acetiloctahidro-2H-pirazino[1,2-a]pirazin-2-il]-4-(4-fluoro-2-metilfenilo)-3-piridinil]-2-[3,5-bis(trifluorometilo)fenil]-N,2-dimetilpropanamida (enantiómero 2) o una sal farmacéuticamente aceptable del mismo, en donde "enantiómero 2" significa un solo enantiómero de estereoquímica absoluta desconocida preparado de conformidad con el ejemplo 72 descrito aquí.

30.- Un procedimiento para la preparación de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo de conformidad con cualquiera de las reivindicaciones 1 a 29, el procedimiento comprende: (a) hacer reaccionar un compuesto de la fórmula (II)



(II)

en donde R^3, R^4, R^5, R^6 y s son como se definió antes y L^1 representa un grupo residual adecuado tal como un átomo de halógeno (v.gr., cloro), con un compuesto de la fórmula (III)



(III)

o un derivado opcionalmente protegido del mismo, en donde R^1, R^2, m, n, p, q, X, Y, Z y A son como se definió antes; opcionalmente después seguido por (b) desprotección de un compuesto de la fórmula (I) que es protegido; y (c) interconversión a otros compuestos de la fórmula (I).

31.- Una composición farmacéutica que comprende el compuesto de la fórmula (I) como se define en cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable o excipiente.

32.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 29 para usarse en terapia.

33.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 29 para usarse en el tratamiento de trastornos psicóticos.

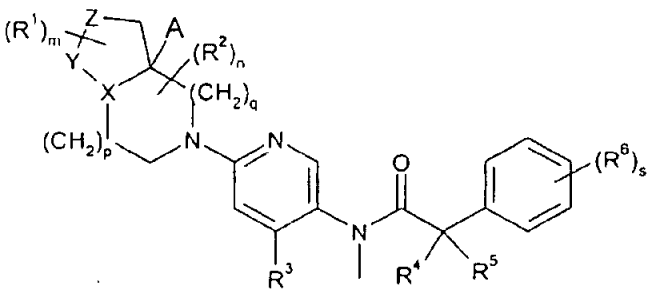
34.- El uso de un compuesto como se reclama en cualquiera de las reivindicaciones 1 a 29 en la fabricación de un medicamento para el tratamiento de trastornos psicóticos.

35.- Un método de tratamiento de trastornos psicóticos que comprende administrar a un hospedero que necesita el mismo una cantidad efectiva de un compuesto de la fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo.

36.- Una composición farmacéutica para usarse en el tratamiento de trastornos psicóticos que comprende el compuesto de la fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 29 o una sal farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable.

RESUMEN DE LA INVENCION

De conformidad con la invención, se proveen compuestos novedosos de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos:



(I)

en donde: X representa un átomo de nitrógeno; Y representa $-C(H_2)-$, $(-C(H_2)-)_2$. $-S(O_2)-$ o $-C(=O)-$; Z representa $-C(H_2)-$, $-S(O_2)-$, $-N(R^Z)-$, o un átomo de oxígeno o azufre; A representa hidrógeno o $-CH_2OH$; R^z representa hidrógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, $-COR^7$ o $-SO_2R^7$; R^1 representa halógeno, alquilo de C_{1-6}, alcoxi de C_{1-6}, =O, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6}, hidroxilo o $-CH_2OH$; m representa un entero de 0 a 3; R^2 representa halógeno, =O, alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), $-COOR^7$, $-CONR^7R^8$, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6} o alquilo de C_{1-6}-O- alquilo de C_{1-6}; n representa un entero de 0 a 3; p y q independientemente representan un entero de 0 a 2; R^3 representa un grupo -arilo, -heteroarilo, -heterociclilo, -aril-arilo, -aril-heteroarilo, -aril-heterociclilo, -heteroaril-arilo, -heteroaril-heteroarilo,

-heteroaril-heterociclilo, -heterociclil-arilo, -heterociclil-heteroarilo o -heterociclil-heterociclilo, todos los cuales pueden ser opcionalmente sustituidos por uno o más (v.gr., 1, 2 ó 3) halógeno, grupos alquilo de C_{1-6} (opcionalmente sustituido por uno o más grupos hidroxilo), cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, hidroxilo, halogenoalquilo de C_{1-6}, halogenoalcoxi de C_{1-6}, ciano, -S-alquilo de C_{1-6}, -SO-alquilo de C_{1-6}, -SO_2-alquilo de C_{1-6}, -COR^7, -$CONR^7R^8$, -NR^7R^8, NR^7CO-alquilo de C_{1-6}, NR^7SO_2-alquilo de C_{1-6}, alquilo de C_{1-6}-NR^7R^8, -$OCONR^7R^8$, -$NR^7CO_2R^8$ o -$SO_2NR^7R^8$; R^4 y R^5 independientemente representa alquilo de C_{1-6}, o R^4 y R^5 junto con el átomo de carbono al cual están unidos juntos pueden formar un grupo cicloalquilo de C_{3-8}; R^6 representa halógeno, alquilo de C_{1-6}, cicloalquilo de C_{3-8}, alcoxi de C_{1-6}, halogenoalquilo de C_{1-6} o halogenoalcoxi de C_{1-6}; s representa un entero de 0 a 4; R^7 y R^8 independientemente representa hidrógeno, alquilo de C_{1-6} o cicloalquilo de C_{3-8}; o solvatos de los mismos.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
GLAXOSMITHKLINE
Attn. Dolton, Peter
Corporate Intellectual Property
CN925.1
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

GlaxoSmithKline Corporate IP Received BRENTFORD 18 JAN 2007
ATTY: TXC
IPM DOCKETING
ATTY CHECKLIST FILE

CORPORATE INTELLECTUAL PROPERTY 23 GEN 2007 VERONA File

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION
(PCT Rule 44.1)

Applicant's or agent's file reference TXC/PB61616	Date of mailing (day/month/year) 18/01/2007 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP2006/008845	International filing date (day/month/year) 07/09/2006
Applicant SMITHKLINE BEECHAM CORPORATION	19 JAN 2007

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Josef Ullrich

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

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.
TXC/PB61616		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2006/008845	07/09/2006	09/09/2005
Applicant		
SMITHKLINE BEECHAM CORPORATION		

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:

   PYRIDINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF PSYCHOTIC DISORDERS

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/008845

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 claim 35 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the 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
PCT/EP2006/008845

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D513/04 C07D487/04 C07D498/04 A61K31/4985 A61K31/5383
A61K31/542 A61K31/4439 A61K31/551 A61P25/00

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/002577 A (HOFFMANN LA ROCHE [CH]; HOFFMANN TORSTEN [DE]; KOBLET ANDREAS [CH]; PE) 13 January 2005 (2005-01-13) cited in the application page 4, line 10 - line 13; claims 46-50,52,53	1-36
Y	WO 03/066621 A1 (GLAXO GROUP LTD [GB]; ALVARO GIUSEPPE [IT]; DI FABIO ROMANO [IT]) 14 August 2003 (2003-08-14) page 9, line 16 - line 18; claims 1,12	1-36
Y	WO 03/066635 A (GLAXO GROUP LTD [GB]; ALVARO GIUSEPPE [IT]; DI FABIO ROMANO [IT]; TRAN) 14 August 2003 (2003-08-14) page 14, line 32 - line 34; claim 1	1-36

☐ 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
5 January 2007	18/01/2007

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	MORIGGI, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/008845

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005002577 A	13-01-2005	AU 2004253267 A1	13-01-2005
		BR PI0412291 A	19-09-2006
		CA 2530886 A1	13-01-2005
		CN 1852712 A	25-10-2006
		KR 20060030893 A	11-04-2006
		MX PA06000192 A	11-04-2006
		US 2005090533 A1	28-04-2005
WO 03066621 A1	14-08-2003	AU 2003207023 A1	02-09-2003
		EP 1472243 A1	03-11-2004
		JP 2005524636 T	18-08-2005
		US 2005096313 A1	05-05-2005
WO 03066635 A	14-08-2003	AT 308543 T	15-11-2005
		AU 2003205753 A1	02-09-2003
		BR 0307123 A	07-12-2004
		CA 2475619 A1	14-08-2003
		CN 1628115 A	15-06-2005
		DE 60302137 D1	08-12-2005
		DE 60302137 T2	20-07-2006
		DK 1472256 T3	20-03-2006
		EP 1472256 A1	03-11-2004
		ES 2250870 T3	16-04-2006
		IS 7382 A	04-08-2004
		JP 2005524637 T	18-08-2005
		MX PA04006791 A	06-12-2004
		US 2005176715 A1	11-08-2005
		ZA 200404842 A	26-07-2005

PATENT COOPERATION TREATY

661

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/EP2006/008845	07.09.2006	09.09.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D513/04 C07D487/04 C07D498/04 A61K31/4985 A61K31/5383 A61K31/542 A61K31/4439 A61K31/551 A61P25/00

Applicant
SMITHKLINE BEECHAM CORPORATION

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	MORIGGI, J Telephone No. +49 89 2399-2692

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/008845

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

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

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

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

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/EP2006/008845

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. 35 (Industrial Applicability)

because:

☒ the said international application, or the said claims Nos. 35 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/EP2006/008845

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	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-34, 36
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claim 35 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V.

1. Reference

Reference is made to the following documents:

D1 : WO 2005/002577 –
D2 : WO 03/066621
D3 : WO 03/066635 –

2. Novelty

Prior art document D1 discloses pyridine derivatives useful for treating schizophrenia. The groups R^4 and R^5 of the compounds of formula (I) of claim 1 of D1 can form, together with the nitrogen to which they are attached, a monocyclic, a bridged or a spiro-fused ring system but no ortho-fused rings as disclosed in the present application.

Prior art documents D2 and D3 disclose piperidine derivatives useful in the treatment of schizophrenia. The compounds of formula (I) of the present invention differ however from those of D2 and D3 in the presence of a pyridine instead of a piperidine.

The subject-matter of claims 1-36 therefore appears to be new in the sense of Article 33(2) PCT.

3. Inventive Step

Document D3 is regarded as being the closest prior art to the subject-matter of claim 1. D3 discloses piperidine derivatives useful in the treatment of schizophrenia.

As previously mentioned, the subject-matter of claim 1 therefore differs from D3 in the presence of a pyridine instead of a piperidine and a reversed amide.

The problem to be solved by the present invention may therefore be regarded as how to

provide further compounds useful in the treatment of schizophrenia.

The biological data provided on page 185 of the description seem to indicate that the compounds of formula (I) of claim 1 of the present application actually solve the technical problem.

However, in view of documents D1 and D2, it would appear obvious to the person skilled in the art confronted to the problem of providing further compounds useful in the treatment of schizophrenia that the central units pyridine-N-CO and piperidine-CO-N are equivalent features. As a result, starting from the compounds of formula (I) of claim 1 of D3, the skilled person would have replaced the piperidine-CO-N moiety with pyridine-N-CO, thereby arriving at the compounds of formula (I) of the present invention.

As a result, the problem underlying the present application can no longer be seen in simply the provision of further compounds useful in the treatment of schizophrenia but in the provision of further compounds useful in the treatment of schizophrenia that possess unexpected properties over those of the closest prior art D3. In the absence of comparative test results or other appropriate information, the modification made by the applicant appears to be arbitrary and it is not possible to decide whether such a problem has been solved or not.

The present application does not therefore appear to involve an inventive step in the sense of Article 33(3) PCT.

4. Industrial Applicability

The subject-matter of claims 1-34 and 36 appears to be industrially applicable in the sense of Article 33(4) PCT.

5. Remarks

Claims 26 and 29 do not meet the requirements of rule 6.2 (a) PCT, whereby reference to the description is not allowed, except where absolutely necessary.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] 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 [ ]

Adriana Betancur

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
SMITHKLINE BEECHAM CORPORATION

REFERENCIA	Radicación No.	8 24576
	Solicitud internacional	PCT/EP2006/008845
	Fecha inicio fase nacional	09/04/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	5224

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

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

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

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

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

El anterior requerimiento fue notificado por fijación en lista de fecha 10 ABR. 2008
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