06-78323

Libertad y Orden

REPÚBLICA DE COLOMBIA

DIVISIÓN DE PROPIEDAD INDUSTRIAL

PCT

PATENTE DE INVENCIÓN

Industria y Comercio
SUPERINTENDENCIA

06-78323

TITULO: ANTAGONISTAS DEL RECEPTOR DE QUIMIOCINA

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza.

APODERADO: CARLOS R. OLARTE

BOGOTÁ, agosto 9 de 2006

P2006/000150

SS

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radi: 06-078323- -00000-0000
Fec: 2006-09-09 17:30:39 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEINVI
Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 580

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 11/09/06

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel, Suiza.
Nacionalidad o Domicilio: SUIZA
Lugar de Constitución: SUIZA
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PÁGINA ADJUNTA Ver Folio 3
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2005/001362 Fecha Febrero 10, 2005

Publicación Internacional No. WO 2005/077932 Fecha Agosto 25, 2005

(6) **Título (54)** ANTAGONISTAS DEL RECEPTOR DE QUIMIOCINA

Clasificación Internacional (51) C07D 401/00 A61K 31/04, A61P 31/18.

Prioridad SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Febrero 11, 2004	0403038.3

(9) **Comprobante de pago No.** 06 – 58,179 **Fecha** Agosto 1, 2006

(10) ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:

(12) 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.

LISTA DE INVENTORES PCT/EP2005/001362

RENE HERSPERGER;
Höhenweg 32, CH-4142 Münchenstein
Suiza
Nacionalidad: Suiza

PHILIPP JANSER
Delsbergerallee 1,
CH-4053 Basel
Suiza
Nacionalidad: Suiza

EMIL PFENNINGER
Schoenenbuchstrasse 92,
CH-4123 Allschwil
Suiza
Nacionalidad: Suiza

HANS JUERG WUETHRICH
Fluhmattweg 11,
CH-3122 Kehrsatz
Suiza
Nacionalidad: Suiza

WOLFGANG MILTZ
Tessinstrasse 12,
CH-4054 Basel
Suiza
Nacionalidad: Alemana

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-078323- -00000-0000
Fec: 2006-08-09 17:30:38 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEYYII
Eve: 379 FABENACIONALI
Act 411 PRESENTACION Folios: 000

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 58,179
FECHA : AGOSTO 1 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECR	CONSIGNACION	BANCO POPULAR	050-00110-6	52198837	01/08/2006	2,612,000.00

***** 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	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 August 2005 (25.08.2005)

PCT

(10) International Publication Number
WO 2005/077932 A2

(51) International Patent Classification[7]: C07D 401/00

(21) International Application Number:
PCT/EP2005/001362

(22) International Filing Date: 10 February 2005 (10.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0403038.3 11 February 2004 (11.02.2004) GB

(71) Applicant (*for all designated States except AT, US*): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (*for AT only*): NOVARTIS PHARMA GmbH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): HERRPERGER, René [CH/CH]; Höhenweg 32, CH-4142 Münchenstein (CH). JANSER, Philipp [CH/CH]; Delsbergerallee 1, CH-4053 Basel (CH). PFENNINGER, Emil [CH/CH]; Schoenenbuchstrasse 92, CH-4123 Allschwil (CH). WUETHRICH, Hans, Juerg [CH/CH]; Fluhmattweg 11, CH-3122 Kehrsatz (CH). MILTZ, Wolfgang [DE/CH]; Teufinstrasse 12, CH-4054 Basel (CH).

(74) Agent: LEON, Susanna; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

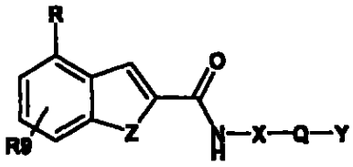
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,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

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, 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, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

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

(54) Title: CHEMOKINE RECEPTOR ANTAGONISTS



(I)

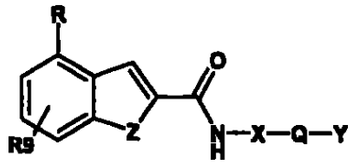
(57) Abstract: A compound of formula (I) or a pharmaceutically acceptable salt or prodrug ester thereof, wherein the variants R, R9, Z, X, Q and Y are defined in the specification.

WO 2005/077932 A2

Chemokine Receptor Antagonists

The invention relates to bicyclic carbonyl amino derivatives which are antagonists of Chemokine Receptor 2 (CCR-2) and Chemokine Receptor 5 (CCR-5), and to their use in the treatment of diseases and disorders which involve migration and activation of monocytes and T-cells, including inflammatory diseases.

Accordingly the invention in a first aspect provides a compound of formula (I), or a pharmaceutically acceptable salt or prodrug ester thereof:



(I)

Wherein:

Z is CR_1R_2, NR_3, O or S;

R is selected from the group consisting of hydroxy, an optionally substituted C_1-C_7 alkoxy, C_2-C_7 alkenoxy, cycloalkyloxy, aryloxy, heteroaryloxy, aryl- C_1-C_7 alkoxy or heteroaryl- C_1-C_7 alkoxy, an optionally substituted C_1-C_7 alkyl or C_2-C_7 alkenyl, an optionally substituted aryl, heteroaryl or an optionally substituted aryl- C_1-C_7 alkyl group;

R9 represents one or more ring substituents selected from the group consisting of H, hydroxy, an optionally substituted C_1-C_7 alkoxy, C_2-C_7 alkenoxy, cycloalkyloxy, aryloxy, heteroaryloxy, aryl- C_1-C_7 alkoxy or heteroaryl- C_1-C_7 alkoxy, an optionally substituted C_1-C_7 alkyl or C_2-C_7 alkenyl, an optionally substituted aryl, heteroaryl or an optionally substituted aryl- C_1-C_7 alkyl group;

R_1, R_2, and R_3 are independently selected from the group consisting of H and C_1-C_7 alkyl;

X is a C_3-C_{18} cycloalkyl, heterocycloalkyl, aryl or heteroaryl each of which may be optionally substituted;

Q is a linker of between 1 and 3 atoms in length;

Y is C_3-C_{18} cycloalkyl, heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, aryl, heteroaryl, fused aryl-heterocycloalkyl, all of which are independently optionally substituted once or more;

The optional substituent or substituents on R and R9 are independently selected from the group consisting of halogen, hydroxy, C_1-C_7 alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl.

The optional substituent or substituents on X are independently selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl.

The optional substituent or substituents on Y are independently selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents,

selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_5-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl.

For the avoidance of doubt, the terms listed below are to be understood to have the following meaning throughout the present description and claims:

The term "lower", when referring to organic radicals or compounds means a compound or radical with may be branched or unbranched with up to and including 7 carbon atoms.

A lower alkyl group may be branched, unbranched or cyclic and contains 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms. Lower alkyl represents, for example: methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tertiary butyl or 2,2-dimethylpropyl.

A lower alkoxy group may be branched or unbranched and contains 1 to 7 carbon atoms, preferably 1 to 6 carbon atoms. Lower alkoxy represents, for example: methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or tertiary butoxy. Lower alkoxy includes cycloalkyloxy and cycloalkyl - lower alkyloxy.

A lower alkene, alkenyl or alkenoxy group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1 to 4 carbon atoms and contains at least one carbon-carbon double bond. Lower alkene, lower alkenyl or lower alkenyloxy represents for example vinyl, prop-1-enyl, allyl, butenyl, isopropenyl or isobutenyl and the oxy equivalents thereof.

In the present application, oxygen containing substituents, e.g. alkoxy, alkenyloxy, alkynyloxy, carbonyl, etc. encompass their sulphur containing homologues, e.g. thioalkoxy, thioalkenyloxy, thioalkynyloxy, thiocarbonyl, sulphone, sulphoxide etc.

Halo or halogen represents chloro, fluoro, bromo or iodo.

Aryl represents carbocyclic aryl, heterocyclic aryl or biaryl.

Carbocyclic aryl is an aromatic cyclic hydrocarbon containing from 6 to 18 ring atoms. It can be monocyclic, bicyclic or tricyclic, for example naphthyl, phenyl, or phenyl mono-, di- or trisubstituted by one, two or three substituents.

Heterocyclic aryl is an aromatic monocyclic or bicyclic hydrocarbon containing from 5 to 18 ring atoms one or more of which are heteroatoms selected from O, N or S. Preferably there are one or two heteroatoms. Heterocyclic aryl represents, for example: pyridyl, indolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl. Heterocyclic aryl also includes such substituted radicals.

Cycloalkyl represents a cyclic hydrocarbon containing from 3 to 12 ring atoms preferably from 3 to 6 ring atoms. Cycloalkyl represents, for example: cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The cycloalkyl may optionally be substituted.

Heterocycloalkyl represents a mono-, di- or tricyclic hydrocarbon which may be saturated or unsaturated and which contains one or more, preferably one to three heteroatoms selected from O, N or S. Preferably it contains between three and 18 ring atoms. The term heterocycloalkyl is intended also to include bridged heterocycloalkyl groups such as 3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl.

Pharmaceutically acceptable prodrug esters are ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acid of formula (I). Such esters are for example lower alkyl esters (such as methyl or ethyl esters), carboxy-lower alkyl esters such as the carboxymethyl ester, nitrooxy-lower alkyl esters (such as the 4-nitrooxybutyl ester).

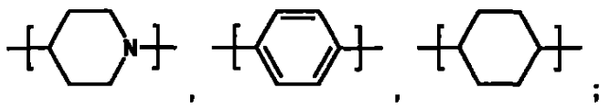
Referring to formula (I), preferably Z is NH, NCH_3, CH_2, S or O.

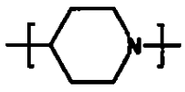
R is preferably hydroxy, an optionally substituted lower alkoxy, alkenoxy, cycloalkyl-lower alkyloxy, aryloxy, heteroaryloxy, aryl-lower alkyloxy or heteroaryl lower alkyloxy, an optionally substituted aryl, heteroaryl or an optionally substituted aryl-lower alkyl group.

More preferably, R is an oxy group, e.g. C_1-C_7 alkoxy. Yet more preferably, R is a branched C_1-C_7 alkoxy or a substituted C_1-C_7 alkoxy. A preferred substituent for the substituted C_1-C_7 alkoxy is a furyl or benzofuryl which is optionally substituted.

R9 is preferably hydrogen.

X is preferably selected from the group consisting of:



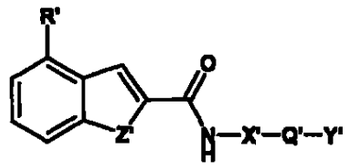
Most preferably, X is  .

Q is preferably defined by $-CR_4R_5-$ or $-CR_4R_5-Q_1-$ wherein Q_1 denotes $-CR_6R_7-$ or $-NR_6-$; R_4, R_5, R_6 and R_7 and R_8 being independently selected from the group consisting of H, an optionally substituted lower alkyl, an optionally substituted lower alkenyl, an optionally substituted aryl or an optionally substituted aryl-lower alkyl group, for example methyl, $(CH_3)_2CH-CH_2-$, $CH_3-C(=CH_2)-CH_2-$, $(CH_3)_3C-CH_2-$, benzyl;

Q is more preferably selected from the group consisting of: $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH_2-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$, $-CH_2-CH(CH_2OH)-$ or $-CH(CH_3)-NH(CH_3)-$;

Y is preferably selected from the group consisting of: piperidinyl, azepanyl, azocanyl, phenyl, tetrahydropyranyl, 8-aza-bicyclo[3.2.1]oct-8-yl, tetrahydropyridinyl, octahydroquinolizinyl, hexahydro-pyrrolooxazinyl, octahydro-pyridooxazinyl each of which is optionally substituted. Preferred optional substituents for Y are: hydroxy, amino, halo, C_1-C_7 alkyl.

A second aspect of the invention provides a compound of formula (II), or a pharmaceutically acceptable salt, ester or prodrug thereof:



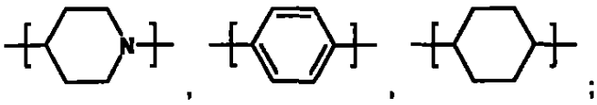
(II)

wherein:

Z' is NH, NCH_3, CH_2, S or O.

R' is hydroxy, an optionally substituted C_1-C_7 alkoxy, cycloalkyl- C_1-C_7 alkyloxy, aryloxy, heteroaryloxy or aryl- C_1-C_7 alkyloxy, an optionally substituted aryl, heteroaryl or an optionally substituted aryl-C_1-C_7 alkyl group;

X' is selected from the group consisting of:



Q' is selected from the group consisting of: $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH_2-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$, $-CH_2-CH(CH_2OH)-$ or $-CH(CH_3)-NH(CH_3)-$;

Y' is C_3-C_{18} cycloalkyl, heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, aryl, heteroaryl, fused aryl-heterocycloalkyl, all of which are independently optionally substituted once or more;

the optional substituent or substituents on R' being independently selected from the group consisting of halogen, hydroxy, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di-C_1-C_7 alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, C_1-C_7

alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on Y' being independently selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl.

Preferred compounds of formula I are:

4-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(RS)-2-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((2S,6R)-2,6-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((R)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((S)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((1R,3S,5S)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [4-(2-azepan-1-yl-ethyl)-phenyl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-[[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-cyclohexyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-[[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-{(R)-1-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl}-phenyl)-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-((1R,3S,5S)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(3-Methyl-butyloxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methyl-pentyloxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(3,3-Dimethyl-butoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(Furan-2-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Benzyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3R,4R,5S)-4-hydroxy-3,5-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(7-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3R,4R,5S)-4-hydroxy-3,5-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(5-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Phenoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(3-RS-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide dihydrochloride

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(1-methyl-piperidin-3-ylmethyl)-piperidin-4-yl]-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3R,4R)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4R,5S)-3,4-dihydroxy-5-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(R)-3-hydroxy-2-((3S,4S)-4-ydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3R,4R)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(2-Methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(3,4-dihydroxy-5-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3RS,4SR)-3,4-dihydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3RS,4SR)-3,4-dihydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(9S,9aS)-1-(octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)methyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(8S,8aS)-1-(hexahydro-pyrrolo[2,1-c][1,4]oxazin-8-yl)methyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1S-methyl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1*R*-methyl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2*S*-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2*R*-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3,6-dihydro-2H-pyridin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-amino-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-fluoro-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [4-(2-piperidin-1-yl-ethyl)-phenyl]-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {4-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-phenyl}-amide

4-Phenyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethyl-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Dimethylamino-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,2,5]oxadiazol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Cyano-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-[3-(3-Methoxy-propoxy)-phenyl]-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(2,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,3]dioxol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Pyridin-4-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Hydroxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

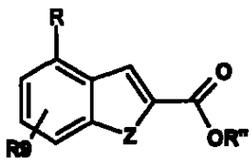
4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-benzofuran-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

According to a third aspect of the invention there is provided a compound of formula (I) for use as a pharmaceutical for the prevention, amelioration or treatment of an autoimmune or inflammatory disease or condition.

According to a fourth aspect of the invention there is provided a process for the preparation of a compound of formula (I) comprising:

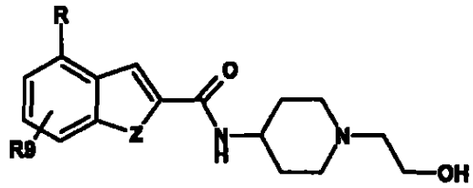
(a) reacting a compound of formula (III):



(III)

wherein R" is H or a lower alkyl group, with a compound of formula NH_2-X-Q-Y, the groups R, R9, Z, X, Q and Y being defined above; or

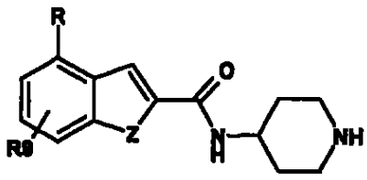
(b) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is $-CH_2-CH_2-$, and Y is a group having the formula $-NR_7R_8$ wherein N, R_7 and R_8 are linked to define collectively a heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, heteroaryl, or fused aryl-heterocycloalkyl, reacting a compound of formula (IV):



(IV)

with a compound of formula NHR_7R_8, wherein R_7 and R_8 are as defined above, and R, R9 and Z are as defined earlier; or

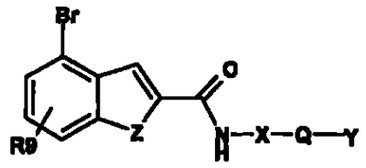
(c) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is CH_2-, reacting a compound of formula (V):



(V)

in which R, R9 and Z are as defined above, with a compound of formula HO-CH_2-Y, in which Y is as defined earlier; or

(d) for the preparation of compounds of formula (I) wherein R is an optionally substituted aryl group, appropriately substituting the Br group in a compound of formula (VI) for said substituted aryl group:



(VI)

wherein Z, R9, X, Q and Y are as earlier defined;

and recovering the resultant compounds of formula (I) in free or salt form.

The process of the invention is effected in conventional manner.

Process variant (a) is a condensation reaction between acid or ester and amine. It is conveniently effected by reacting the acid with the amine in the presence of coupling agents, for example TBTU/DIEA in a solvent such as DMF, or by reacting the ester with the amine in the presence of a coupling agent such as HOBT/EDC.

Process variant (b) is a condensation reaction which is conveniently carried out using a reagent such as cyanomethyl-triphenyl phosphonium iodide and Hunig's base.

Process variant (c) is a condensation reaction is also a condensation reaction which is conveniently carried out using a reagent such as cyanomethyl-triphenyl phosphonium iodide and Hunig's base.

Process variant (d) is a substitution reaction and is conveniently effected using the appropriate aryl-boronic acid and triphenylphosphine in the presence of lead (II) acetate.

The compounds of the invention can be recovered from the reaction mixture and purified in conventional manner. Isomers, such as enantiomers, may be obtained in conventional manner, e.g. by fractional crystallization or asymmetric syntheels from corresponding asymmetrically substituted, e.g. optically active, starting materials.

The starting materials and intermediates are either known or can be prepared according to known methods or analogously as described in the Examples.

According to a fifth aspect of the invention there is provided compound obtainable by any one of the above mentioned processes.

According to a sixthaspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I) in association with a pharmaceutically acceptable diluent or carrier.

According to a seventh aspect of the invention there is provided the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of an autoimmune or inflammatory disease or condition.

According to an eighth aspect of the invention there is provided a method of inhibiting chemokine receptors or macrophage proteins or of reducing inflammation in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula (I).

According to a ninth aspect of the invention there is provided a method of treating an inflammatory or autoimmune disease or condition, comprising administering to said subject an effective amount of a compound of formula (I).

Agents of the invention may be prepared by processes described below:

EXPERIMENTAL SECTION

Abbreviations:

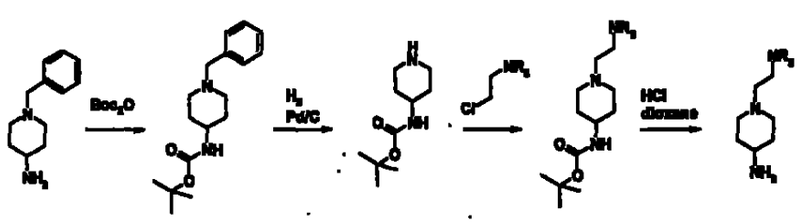
BOC:	t-Butyloxycarbonyl
Boc2O:	Di-t-butyl dicarbonate
DCC:	Dicyclohexyl-carbodiimide
DCE:	Dichloroethane
DCM:	Dichloromethane
DEAD:	Diethyl azadicarboxylate
DIEA:	Ethyl-diisopropyl-amine
DMAP:	Dimethyl-pyridin-4-yl-amine
DME:	1,2-Dimethoxy-ethane
DMF:	N,N-Dimethyl formamide
EDC:	(3-Dimethylamino-propyl)-ethyl-carbodiimide hydrochloride
Ether:	Ethoxy-ethane
EtOH:	Ethanol
EtOAc:	Acetic acid ethyl ester
HCl:	Hydrochloric acid
HOBT:	Benzotriazol-1-ol
LAH:	Lithium aluminumhydride
LDA:	Lithium diisopropylamine
MeOH:	Methanol
NaOH:	Sodium hydroxide
NMP:	1-Methyl-pyrrolidin-2-one
Pd/C:	Palladium on carbon
TBAF:	Tetrabutylammonium fluoride
TBME:	t-Butyl-methyl ether
TBDMS:	t-Butyl-dimethyl-silyl
TBTU	O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
t-BuOH	2-Methyl-propan-2-ol
TFA:	Trifluoro-acetic acid
THF:	Tetrahydrofuran

1H-NMR spectra are recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) and number of protons. Electron Spray Ionization (ESI) mass spectra are recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge. Preparative HPLC purifications are performed with XTerraTM RP18 19x150mm columns, using acetonitrile/water or MeOH/water as eluent systems. All reagents, starting materials and intermediates utilized in these examples are available from commercial sources or are readily prepared by methods known to those skilled in the art.

Synthesis of the amine building blocks

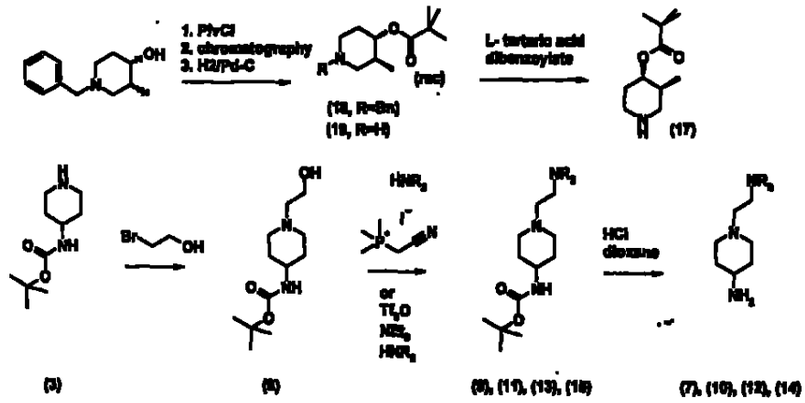
The amines 1, 5, 7, 10, 12, 14, 17, 20, 21, 24, 27, 30, 35, 41, 50, 56, 60, 61, 63, 67, 70 and 72 are prepared according the reaction schemes outlined below.

Reaction Scheme 1:

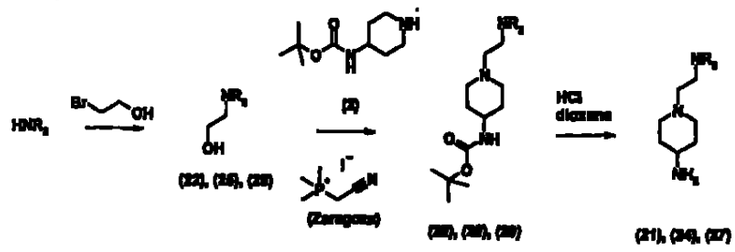


(3) (2) (4), (5) (1), (6)

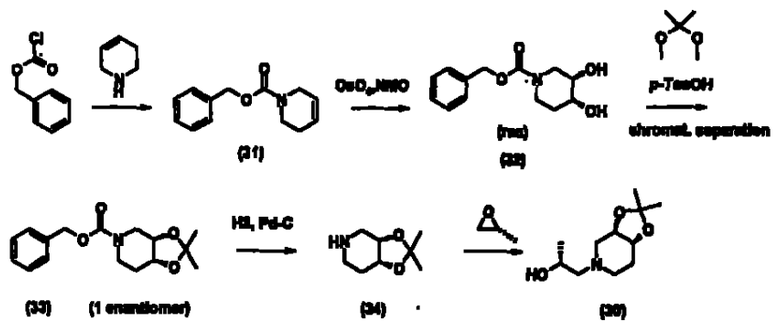
Reaction Scheme 2:



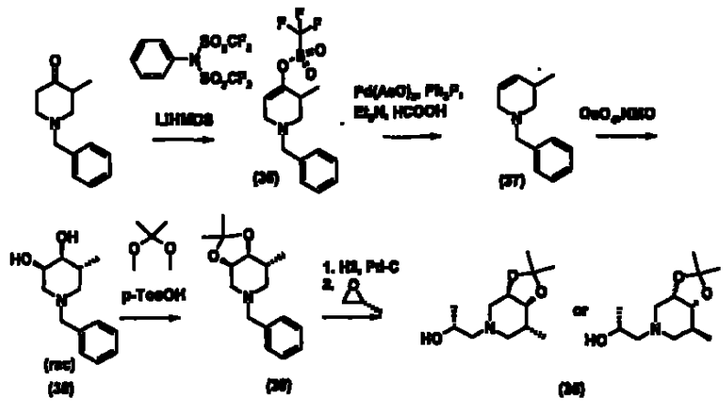
Reaction Scheme 3:



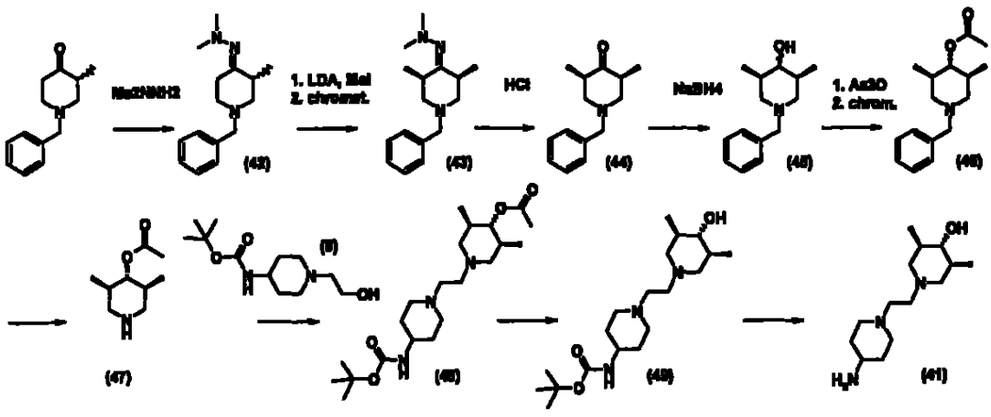
Reaction Scheme 4:



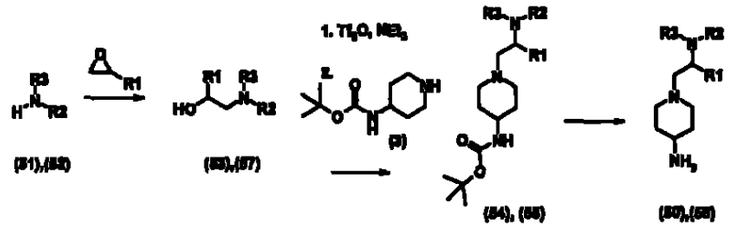
Reaction Scheme 5:



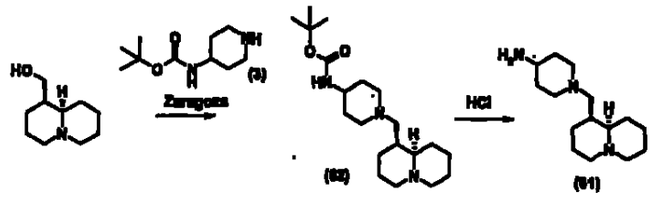
Reaction Scheme 6:



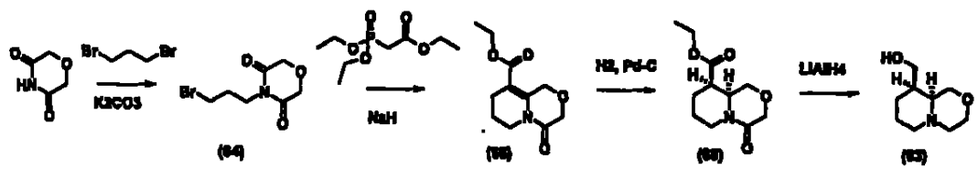
Reaction Scheme 7:



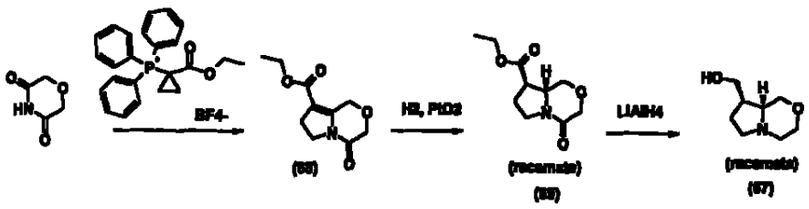
Reaction Scheme 8:



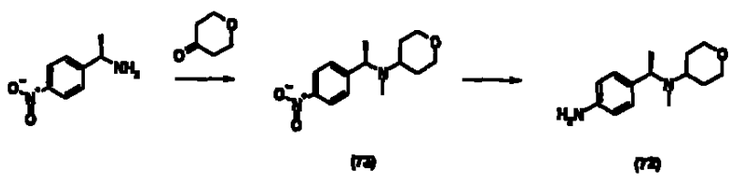
Reaction Scheme 9:



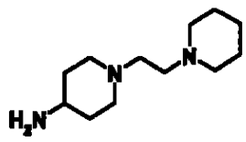
Reaction Scheme 10:



Reaction Scheme 11:



Synthesis of 1-(2-Piperidin-1-yl-ethyl)-piperidin-4-ylamine tri-hydrochloride (1) (reaction scheme 1):



(1) (1-Benzyl-piperidin-4-yl)-carbamic acid tert-butyl ester (2)

1-Benzyl-piperidin-4-ylamine (50 g, 262.76 mmol) is dissolved in a mixture of 200 ml of water, 145 ml of 2 molar aqueous sodium hydroxide and 350 ml of t-BuOH at 0°C. A solution of Boc2O (83.1 g, 1.1 equivalents) in 150 ml of t-BuOH is added dropwise within one hour at 0°C. A white suspension is formed which is allowed to stir overnight at room temperature. The reaction mixture is diluted with ether and washed with water,. The organic layers are dried over anhydrous sodium sulfate and evaporated under reduced pressure.
Yield: 71.5 g of a pale yellow solid (93%). MS (ESI): 291 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.2–7.35 (m, 5H), 6.77 (br d, 1H), 3.44 (s, 2H), 3.22 (br m, 1H), 2.75 (m, 2H), 1.95 (dt, 2H), 1.68 (m, 2H), 1.38 (s, 9H), 1.36 (dt 2H).

(2) Piperidin-4-yl-carbamic acid tert-butyl ester (3)

A solution of the ester 2 from above (66 g, 227.27 mmol) in 1 l of ethanol is hydrogenated under normal pressure with 10 g of Pd/C (10%) for 16 hours at room temperature. The mixture is filtered over celite and evaporated under reduced pressure. Recrystallisation from ether gave 34.5 g (76%) of white crystals.
MS (ESI): 201 $[M+H]^+$, 401 [2M+H]+, 1H-NMR (DMSO-d_6): δ (ppm) 6.7 (br d, NH), 3.22 (br m, 1H), 2.88 (dt, 2H), 2.39 (dt, 2H), 1.8 (br s, NH), 1.6 (dt, 2H), 1.35 (s, 9H), 1.18 (dt, 2H).

(3) 1-(2-Piperidin-1-yl-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (4)

Piperidin-4-yl-carbamic acid tert-butyl ester (3) (4.8 g, 23.72 mmol), 1-(2-Chloro-ethyl)-piperidine hydrochloride (5.3 g, 26.09 mmol) and DIEA (8.9 ml, 52.18 mmol) are dissolved in 150 ml of chloroform and refluxed for 18 hours. After addition of more 1-(2-Chloro-ethyl)-piperidine hydrochloride (2.65 g, 13.05 mmol) and DIEA (4.4 ml, 26.09 mmol) the reaction mixture is refluxed for another 4 hours. After cooling to room temperature, the mixture is

diluted with DCM and washed with water and 5% aqueous sodium hydrogen carbonate solution. Evaporation gave 7.3 g of brownish crystals which are recrystallized from ether/hexane.

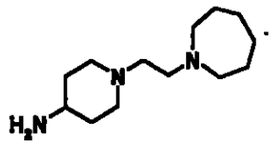
Yield: 5.3 g (72%) of beige crystals. MS (ESI): 312 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.75 (br d, NH), 3.18 (br m, 1H), 2.8 (m, 2H), 2.3-2.4 (m, 8H), 1.92 (dt, 2H), 1.65 (m, 2H), 1.48 (m, 4H), 1.38 (s, 9H), 1.3-1.4 (m, 4H).

(4) 1-(2-Piperidin-1-yl-ethyl)-piperidin-4-ylamine tri-hydrochloride (1)

Ester 4 from above (5.2 g, 16.7 mmol) is suspended at 0°C in 60 ml of a 4M solution of HCl in dioxane and stirred at room temperature for 3 hours. After evaporation under reduced pressure the crude product is dried at high vacuum.

Yield: 5.3 g (99%) of light beige crystals. MS (ESI): 212 $[M+H]^+$, 1H-NMR (D2O): δ (ppm) 4.14 (m, 2H), 4.04 (br m, 5H), 3.8 (m, 4H), 3.65 (dt, 2H), 2.85 (d, 2H), 2.45 (m, 2H), 2.35 (m, 4H), 2.15 (m, 2H).

<u>Synthesis of 1-(2-Azepan-1-yl-ethyl)-piperidin-4-ylamine tri-hydrochloride (5) (reaction scheme 1):</u>



(1) [1-(2-Azepan-1-yl-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (6)

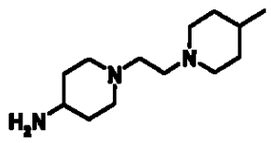
It is synthesized analogously to ester 4 starting from 2-(hexamethyleniminо)ethyl chloride (13.8 g) and ester 3 (12.4 g).

Yield: 14 g of a colorless solid (63%). MS (ESI): 326 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.75 (br d, NH), 3.18 (br m, 1H), 2.8 (m, 2H), 2.3-2.6 (m, 8H), 1.95 (dt, 2H), 1.65 (m, 2H), 1.55 (m, 6H), 1.38 (s, 9H), 1.3-1.4 (m, 4H).

(2) 1-(2-Azepan-1-yl-ethyl)-piperidin-4-ylamine tri-hydrochloride (5)

It is prepared analogously to 1 starting from ester 6 (14 g).
Yield: 13 g (90%) of a colorless solid. MS (ESI): 226 $[M+H]^+$, 1H-NMR (120°C, DMSO-d_6): δ (ppm) 8.5 (br, NH3+), 3.5 (m, 5H), 3.4 (m, 2H), 3.3 (m, 4H), 2.97 (m, 2H), 2.18 (m, 2H), 2.05 (m, 2H), 1.9 (m, 4H), 1.7 (m, 4H).

Synthesis of 1-[2-(4-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine tri-hydrochloride (7) (reaction scheme 2):



(1) **[1-(2-Hydroxy-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (8)**

To a solution of piperidin-4-yl-carbamic acid tert-butyl ester 3 (10 g, 50 mmol) in 100 ml of methanol are added sodium carbonate (21.2 g, 200 mmol) and 2-bromoethanol (7.1 ml, 100 mmol). The mixture is stirred over night. The solvents are then evaporated and the residue is triturated with DCM, filtered and evaporated again. The crude product is purified by chromatography using EtOAc/MeOH (saturated with ammonia) : 9/1.
Yield: 8.07 g (66%). MS (ESI): 245.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.75 (br d, 1H), 4.34 (t, 1H), 3.46 (q, 2H), 3.19 (br m, 1H), 2.8 (m, 2H), 2.35 (t, 2H), 1.95 (m, 2H), 1.66 (m, 2H), 1.39 (s, 9H), 1.35 (m, 2H).

(2) **{1-[2-(4-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (9)**

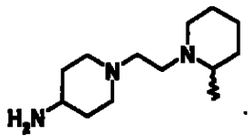
A mixture of ester 8 (3 g, 12.28 mmol), 4-methyl piperidine (1.46 ml, 12.28 mmol) and DIEA (2.7 ml, 15.96 mmol) in 30 ml of propionitrile is treated with solid cyanomethyl-trimethyl-phosphonium iodide (3.58 g, 14.74 mmol) and heated at reflux for 3 hours. After cooling to room temperature, a 2M-K2CO3 solution is added until basic and the mixture is extracted twice with DCM. The organic layers are washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude material is purified by chromatography using EtOAc/MeOH (saturated with ammonia) : 9/1.

Yield: 2 g (50%). MS (ESI): 326.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.74 (br d, 1H), 3.16 (m, 1H), 2.78 (m, 4H), 2.33 (br s, 4H), 1.86 (m, 4H), 1.64 (m, 2H), 1.53 (m, 2H), 1.36 (s, 9H), 1.32 (m, 3H), 1.08 (m, 2H), 0.86 (d, 3H).

(3) 1-[2-(4-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine tri-hydrochloride (7)

The tert-butyl ester 9 (2 g, 6.14 mmol) is suspended in 10 ml of dioxane. DCM is then added until the solid dissolved. To this mixture, 4M-HCl in dioxane (12.3 ml, 49.2 mmol) is added. After stirring over night the solvents are evaporated to leave a white solid product.
Yield: 2.06 g (100%). MS (ESI): 226.2 $[M+H]^+$

<u>Synthesis of 1-[2-((RS)-2-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine tri-hydrochloride (10) (reaction scheme 2):</u>



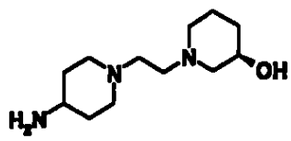
(1) {1-[2-((S)-2-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (11)

It is prepared analogously to 9 starting from tert-butyl ester 8 (2 g, 8.19 mmol), (S)-2-methyl-piperidine (0.985 ml, 8.19 mmol), DIEA (1.8 ml, 10.65 mmol) and cyanomethyl-trimethyl-phosphonium iodide (2.39 g, 9.83 mmol).
Yield: 1.35 g (51%). MS (ESI): 326.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.42 (br d, 1H), 3.47 (m, 1H), 2.84 (m, 4H), 2.47 (m, 3H), 2.15-2.35 (m, 2H), 2.1 (m, 2H), 1.92 (m, 2H), 1.2-1.75 (m, 8H), 1.44 (s, 9H), 1.08 (d, 3H).

(2) 1-[2-((RS)-2-Methyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine tri-hydrochloride (10)

It is prepared by BOC-cleavage of tert-butyl ester 11 (1.3 g, 3.99 mmol) with 4M-HCl in dioxane (8 ml, 32 mmol) as described for amine 7.
Yield: 1.3 g (97%). MS (ESI): 226.2 $[M+H]^+$

Synthesis of (R)-1-[2-(4-Amino-piperidin-1-yl)-ethyl]-piperidin-3-ol tri-hydrochloride (12) (reaction scheme 2):



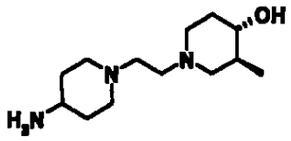
(1) **{1-[2-((R)-3-Hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (13)**

It is prepared analogously to 9 starting from tert-butyl ester 8 (3.52 g, 14.41 mmol), (R)-3-hydroxy-piperidine hydrochloride (2.18 g, 15.85 mmol), DIEA (5.6 ml, 33.14 mmol) and cyanomethyl-trimethyl-phosphonium iodide (4.2 g, 17.29 mmol).
Yield: 1.71 g (36%). MS (ESI): 328.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.61 (br d, 1H), 3.89 (m, 3H), 3.53 (m, 1H), 3.03 (m, 2H), 2.55-2.73 (m, 6H), 2.44 (m, 1H), 2.3 (m, 2H), 1.83-2.02 (m, 3H), 1.5-1.7 (m, 4H), 1.44 (s, 9H).

(2) **(R)-1-[2-(4-Amino-piperidin-1-yl)-ethyl]-piperidin-3-ol tri-hydrochloride (12)**

It is prepared by BOC-cleavage of tert-butyl ester 13 (1.7 g, 5.19 mmol) with 4M-HCl in dioxane (10.4 ml, 41.52 mmol) as described for amine 7.
Yield: 1.69 g (96%). MS (ESI): 228.3 $[M+H]^+$

Synthesis of (3S,4S)-1-[2-(4-Amino-piperidin-1-yl)-ethyl]-3-methyl-piperidin-4-ol tri-hydrochloride (14):



(1) **2,2-Dimethyl-propionic acid (3S,4S)-1-[2-(4-tert-butoxycarbonylamino-piperidin-1-yl)-ethyl]-3-methyl-piperidin-4-yl ester (15)**

A solution of tert-butyl ester 8 (4.8 g, 19.65 mmol) and triethylamine (4.1 ml, 29.47 mmol) in 150 ml of DCM is cooled to -78C. Triflic anhydride (4.3 ml, 25.54 mmol) is slowly added and stirring continued for 1 hour. The mixture is then allowed to warm up to 0C and a solution of

2,2-dimethyl-propionic acid 3*S*-methyl-piperidin-4*S*-yl ester, 17, preparation see below, (3.72 g, 16.66 mmol) in 20 ml of DCM is added at 0C. Stirring is continued at room temperature for 1 hour. The mixture is washed twice with water, dried over sodium sulphate, filtered and evaporated.
Yield: 9.3 g (≥100%, contained some triethylamine). MS (ESI): 426.3 $[M+H]^+$.

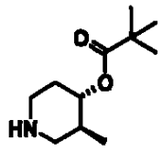
(2) {1-[2-((3S,4S)-4-Hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (16)

Crude 15 (8.2 g, 19.27 mmol) is treated with NaOMe (0.5M in methanol, 77 ml, 38.5 mmol) and heated under reflux for 24 hours. The solvent is then evaporated, the residue taken up in DCM and extracted with 1N-NaOH and brine. Drying and evaporation gave a brown oil which is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 1% to 5%).
Yield: 3.07 g (46%). MS (ESI): 342.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.51 (br d, 1H), 3.5 (br m, 1H), 3.17 (td, 1H), 2.85-3.08 (m, 4H), 2.63 (m, 4H), 2.1-2.35 (m, 3H), 1.48-2.04 (m, 9H), 1.42 (s, 9H), 0.99 (d, 3H).

(3) (3S,4S)-1-[2-(4-Amino-piperidin-1-yl)-ethyl]-3-methyl-piperidin-4-ol tri-hydrochloride (14)

It is prepared by BOC-cleavage of tert-butyl ester 16 (3.07 g, 8.98 mmol) with 4M-HCl in dioxane (11.2 ml, 44.8 mmol) as described for amine 7.
Yield: 3.1 g (98%). MS (ESI): 328.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.61 (br d, 1H), 3.89 (m, 3H), 3.53 (m, 1H), 3.03 (m, 2H), 2.55-2.73 (m, 6H), 2.44 (m, 1H), 2.3 (m, 2H), 1.83-2.02 (m, 3H), 1.5-1.7 (m, 4H), 1.44 (s, 9H).

<u>Synthesis of 2,2-Dimethyl-propionic acid (3S,4S)-3-methyl-piperidin-4-yl ester (17) (reaction scheme 2):</u>



(1) **Step A: *trans*-2,2-Dimethyl-propionic acid 1-benzyl-3-methyl-piperidin-4-yl ester (18)**

To a *cis/trans* mixture of 1-benzyl-3-methyl-piperidin-4-ol (50 g, 243 mmol, prepared as described in *Can. J. Chem.* (1972) 50, 803) in THF is added triethylamine (51 ml, 365 mmol) followed by 2,2-dimethyl-propionyl chloride (45 ml, 365 mmol). The reaction is exothermic and a precipitate is formed. The mixture is heated under reflux for 18 hours, cooled, filtered and washed with ether. The organic layers are washed with 1N-NaOH and brine, dried and evaporated. The crude is purified by chromatography on silicagel using hexane and EtOAc (5%) to give pure *trans*-isomer as a colourless oil.
Yield: 38 g (54%). MS (ESI): 290.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.3 (m, 5H), 4.29 (td, 1H), 3.45 (d, 2H), 2.74 (d, 2H), 2.05 (td, 1H), 1.8 (m, 3H), 1.48 (m, 1H), 1.14 (s, 9H), 0.8 (d, 3H).

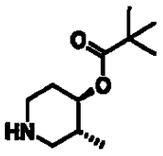
(2) **Step B: *trans*-2,2-dimethyl-propionic acid 3-methyl-piperidin-4-yl ester (19)**

The *trans*-ester 18 (104 g, 359 mmol) is hydrogenated in methanol (1700 ml) with Pd/C in the presence of one equivalent of HCl (431 ml, 359 mmol, 1.25M in MeOH). The mixture is filtered and evaporated. The residue is redissolved in ether and extracted with 1N-NaOH and brine. Evaporation gives a colourless oil.
Yield: 62.7 g (87%). MS (ESI): 200.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.46 (td, 1H), 3.08 (m, 2H), 2.68 (td, 1H), 2.35 (m, 1H), 1.94 (m, 1H), 1.68 (m, 2H), 1.34-1.46 (m, 1H), 1.2 (s, 9H), 0.96 (d, 3H).

(3) **Step C: 2,2-Dimethyl-propionic acid (3S,4S)-3-methyl-piperidin-4-yl ester (17)**

Racemic 19 (62.7 g, 314.4 mmol) is dissolved in EtOAc (300 ml) and a solution of L-(-)-O,O'-Dibenzoyl tartaric acid (56.3 g, 157.2 mmol) in EtOAc (450 ml) is added. The formed solid is filtered off, washed with cold EtOAc and dried. It is then re-crystallized from hot methanol (400 ml). The crystals are collected and the free base is liberated by treatment with 1N-NaOH and extraction with ether.
Yield: 13 g (21%). MS and 1H-NMR are identical to racemic 19. $[\alpha]_D$ = 65.1 (c=1 in MeOH).

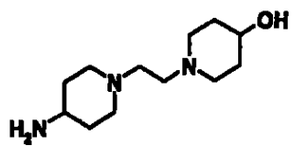
Synthesis 2,2-Dimethyl-propionic acid (3R,4R)-3-methyl-piperidin-4-yl ester (20):



The mother liquor of 17 from above is treated with 1N-NaOH to obtain the free base which is then crystallized with D-(+)-O,O'-Dibenzoyl tartaric acid as described above to give the antipode **20**.

Yield: 16 g (25%). MS and 1H-NMR are identical to racemic **19**. $[\alpha]_D$ = -64.7 (c=1 in MeOH)

Synthesis of 1-[2-(4-Amino-piperidin-1-yl)-ethyl]-piperidin-4-ol tri-hydrochloride (21) (reaction scheme 3):



(1) 1-(2-Hydroxy-ethyl)-piperidin-4-ol (22)

Piperidin-4-ol (5 g, 49.4 mmol) is dissolved in 200 ml of ethanol and anhydrous sodium carbonate (21 g, 197.6 mmol) is added. 2-Bromo-ethanol (6.9 ml, 98.8 mmol) is added dropwise and the reaction mixture is refluxed for 16 hours. After evaporation under reduced pressure the mixture is stirred with 200 ml of DCM and filtered. The clear filtrate is evaporated under reduced pressure und dried at high vacuum.

Yield: 4.3 g (60%) of a colorless oil.

MS (ESI): 146 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.52 (d, 1H), 4.32 (t, 1H), 3.48 (dt, 2H), 3.4 (m, 1H), 2.7 (m, 2H), 2.35 (t, 2H), 2.05 (m, 2H), 1.68 (m, 2H), 1.3-1.4 (m, 2H).

(2) {1-[2-(4-Hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (23)

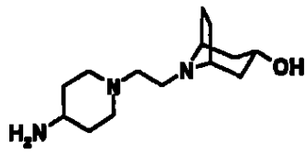
Piperidin-4-yl-carbamic acid tert-butyl ester **3** (5 g, 25 mmol), 1-(2-Hydroxy-ethyl)-piperidin-4-ol **22** (4 g, 27.5 mmol) and DIEA (5.6 ml, 32.5 mmol) are suspended in 25 ml of propionitril. Cyanomethyl-trimethyl-phosphonium iodide (4 g, 30 mmol) is added and the reaction mixture

is refluxed. Additional portions of cyanomethyl-trimethyl-phosphonium iodide (1.5 g, 11.25 mmol) are added after 90 minutes and after 3 hours. After cooling to room temperature, a solution of potassium carbonate (4 g) in 250 ml of water is added and the product is isolated by extraction with DCM. Evaporation under reduced pressure gave 6.9 g of a red oil which could be crystallized from ether.
Yield: 2.2 g (27%) of colorless crystals.
MS (ESI): 328 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.72 (br d, 1H), 4.5 (d, 1H), 3.42 (m, 1H), 3.2 (m, 1H), 2.8 (m, 2H), 2.7 (m, 2H), 2.35 (m, 4H), 2.0 (dt, 2H), 1.9 (dt, 2H), 1.68 (m, 4H), 1.4 (s, 9H), 1.35 (m, 4H).

(3) 1-[2-(4-Amino-piperidin-1-yl)-ethyl]-piperidin-4-ol tri-hydrochloride (21)

Ester 23 (2.2 g, 6.72 mmol) is dissolved in 4M HCl in dioxane at 0°C and stirred at room temperature for 3 hours. After evaporation of the solvent the product is dried at high vacuum.
Yield: 2.3 g (100%) of a white solid. MS (ESI): 228 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 5 (m, 1H), 3.4 (m, 4H), 2.7 (m, 4H), 2.4 (m, 2H), 1.85-2.0 (m, 4H), 1.65 (m, 4H), 1.35 (m, 4H), 1.2 (m, 2H).

Synthesis of 8-[2-(4-Amino-piperidin-1-yl)-ethyl]-8-aza-bicyclo[3.2.1]octan-3-ol tri-hydrochloride (24) (reaction scheme 3):



(1) 8-(2-Hydroxy-ethyl)-8-aza-bicyclo[3.2.1]octan-3-ol (25)

8-Aza-bicyclo[3.2.1]octan-3-ol hydrochloride (5.1 g, 31.45 mmol)) and sodium carbonate (13.3 g, 125.8 mmol) are suspended in 150 ml of ethanol at room temperature. 2-Bromo-ethanol (4.4 ml, 62.9 mmol) is added dropwise within 20 minutes and the reaction mixture is refluxed for 15 hours. After cooling to room temperature the reaction mixture is evaporated under reduced pressure. The mixture is stirred with 200 ml of DCM and filtered. The clear filtrate is dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure und dried at high vacuum.
Yield: 5.4 g (100%) of a colorless oil.

MS (ESI): 172 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.25 (d, 2H), 3.78 (t, 1H), 3.42 (t, 2H), 3.08 (m, 2H), 2.38 (t, 2H), 2.03 (m, 2H), 1.85 (m, 2H), 1.75 (m, 2H), 1.55 (d, 2H).

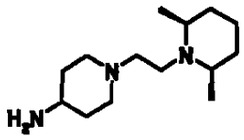
(2) **{1-[2-(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (26)**

Piperidin-4-yl-carbamic acid tert-butyl ester 3 (1 g, 5 mmol), 8-(2-hydroxy-ethyl)-8-aza-bicyclo[3.2.1]octan-3-ol 25 (1 g, 5.5 mmol) and DIEA (1.1 ml, 6.5 mmol) are dissolved in 5 ml of propionitril. Cyanomethyl-trimethyl-phosphonium iodide (792 mg, 6 mmol) is added under stirring and the reaction mixture is refluxed and followed by TLC. Additional cyanomethyl-trimethyl-phosphonium iodide (400 mg) is added after 2 hours and the mixture is refluxed for another hour. After cooling to room temperature, DCM. The combined organic layers are washed with brine, dried over anhydrous a solution of potassium carbonate (4 g) in 250 ml of water is added and the product is isolated by extraction with sodium sulfate, filtered and evaporated under reduced pressure. The crude product (1.9 g) is crystallized from ether. Yield: 940 mg (53%) of light beige crystals. MS (ESI): 354 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.73 (br d, 1H), 4.25 (d, OH), 3.8 (m, 1H), 3.17 (m, 1H), 3.08 (m, 2H), 2.8 (m, 2H), 2.35 (m, 4H), 2.0 (m, 2H), 1.92 (m, 2H), 1.85 (dt, 2H), 1.78 (m, 2H), 1.65 (m, 2H), 1.53 (m, 2H), 1.38 (s, 9H), 1.33 (m, 2H).

(3) **8-[2-(4-Amino-piperidin-1-yl)-ethyl]-8-aza-bicyclo[3.2.1]octan-3-ol tri-hydrochloride (24)**

Ester 26 (4.5 g, 12.73 mmol) is dissolved in 4M HCl in dioxane at 0°C and stirred at room temperature for 3 hours. After evaporation of the solvent the product is dried at high vacuum. Yield: 4.6 g (100%) of a white solid. MS (ESI): 254 $[M+H]^+$.

Synthesis of 1-[2-((2S,6R)-2,6-Dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine tri-hydrochloride (27) (reaction scheme 3):



(1) {1-[2-(2,6-Dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (28)

Compound 28 is prepared analogously to 25 starting from cis-2,6-dimethylpiperidin (6.4 ml, 44.17 mmol) and bromethanol (6.1 ml, 88.33 mmol).
Yield: 3.9 g (56%) of a yellow oil. MS (ESI): 158.1 $[M+H]^+$]+, 1H-NMR (DMSO-d_6): δ (ppm) 4.48 (br, 1H), 3.4 (t, 2H), 2.6 (t, 2H), 2.4 (m, 2H), 1.1-1.8 (m, 6H), 1.03 (d, 6H).

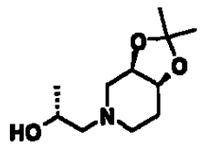
(2) {1-[2-(2,6-Dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (29)

Compound 29 is prepared analogously to 26 starting from compound 28 (3.85 g, 24.48 mmol) and piperidin-4-yl-carbamic acid tert-butyl ester 3 (4.46 g, 22.25 mmol).
Yield: 6.16 g (82%) of a yellow oil. MS (ESI): 340.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.73 (br d, 1H), 3.18 (m, 1H), 2.75 (m, 2H), 2.65 (m, 2H), 2.35 (m, 2H), 2.25 (m, 2H), 1.92 (m, 2H), 1.85 (m, 2H), 1.57 (m, 2H), 1.49 (m, 2H), 1.38 (s, 9H), 1.35 (m, 2H), 1.12 (m, 2H), 1.03 (d, 6H).

(3) 1-[2-((2S,6R)-2,6-Dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-ylamine tri-hydrochloride (27)

Compound 27 is prepared analogously to 24 starting from the BOC protected derivative 29 (6.16 g, 18.14 mmol).
Yield: 6.3 g (100%) of a white solid. MS (ESI): 240.3 $[M+H]^+$.

<u>Synthesis of (R)-1-((3a,7a)-2,2-Dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-5-yl)-propan-2-ol (30) (reaction scheme 4):</u>



(1) 3,6-Dihydro-2H-pyridine-1-carboxylic acid benzyl ester (31)

1,2,3,6-Tetrahydro-pyridine (3 g, 36.1 mmol) are treated with 10% aqueous sodium carbonate (2.1 ml) and cooled to 0°C. Within 1h, benzyl chloroformiate (Z-chloride, 5.1 ml, 36 mmol) is added dropwise within 1h. After additional stirring for 2h, the mixture is treated with 30 ml of brine and extracted four times with diethyl ether. The organic layers are dried over sodium sulphate and evaporated. The crude product, 7 g of a colorless oil, is purified by Flash-chromatography (silica gel, cyclohexane / ethyl acetate 9:1).
Yield: 3.63 g (46%) of a colorless oil. MS (ESI): 218 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.28-7.4 (m, 5H), 5.83 (m, 1H), 5.66 (m, 1H), 5.15 (s, 2H), 3.95 (m, 2H), 3.58 (t, 2H), 2.15 (m, 2H).

(2) 3,4-Dihydroxy-piperidine-1-carboxylic acid benzyl ester (32)

31 (3.63 g, 16.7 mmol) is dissolved in 16 ml of a 1:1 mixture of water and acetone. After addition of N-methyl-morpholine-N-oxide (2.9 g, 24.8 mmol), a 1% solution of osmium tetroxide in tert. Butanol (7.23 ml, 0.28 mmol) is added. The mixture is stirred at room temperature for 20h. Then 70 ml of a saturated sodium bisulfite solution is added. After 15 min stirring at room temperature, the reaction mixture is extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated. The crude product, 4.7 g of a yellow oil, is purified by Flash-chromatography (silica gel, ethyl acetate).
Yield: 3.83 g (91%). MS (ESI): 252 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.27-7.4 (m, 5H), 5.13 (s, 2H), 3.88 (m, 1H), 3.79 (m, 2H), 3.66 (m, 2H), 3.5 (dd, 1H), 3.34 (m, 1H), 2.13 (m, 2H), 1.82 (m, 1H), 1.7 (m, 1H).

(3) 2,2-Dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyridine-5-carboxylic acid benzyl ester (33)

32 from above (3.72 g, 14.8 mmol) is dissolved in 20 ml of dichloromethane. After addition of 2,2-dimethoxypropane (3.6 ml, 30 mmol) and p-toluene sulfonic acid (141 mg, 0.7 mmol) the mixture is stirred at room temperature for 4h. Then the mixture is diluted with 30 ml of dichloromethane, washed subsequently with 1N NaOH and brine, dried over sodium sulphate and evaporated. The crude racemic product, 4.32 g of a yellow oil, is separated into its enantiomers by chiral HPLC (chiralcel, OJ, 20um, hexane / isopropanol 9:1).
Yield: 810 mg peak 1 and 942 mg (peak2) (40%) MS (ESI): 292.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.25-7.4 (m, 5H), 5.14 (s, 2H), 4.18-4.4 (m, 2H), 3.7-3.82 (m, 1H), 3.38-3.58 (m, 3H), 1.74-2.0 (m, 2H), 1.44 (s, 3H), 1.35 (s, 3H).

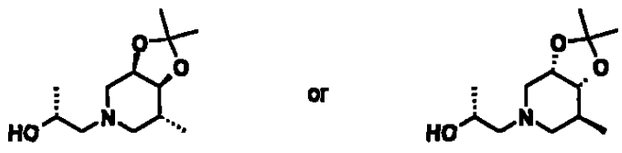
(4) **2,2-Dimethyl-hexahydro-[1,3]dioxolo[4,5-c]pyridine (34)(single cis-enantiomer, absolute configuration unknown)**

33 (peak 1 from above) (450 mg, 1.54 mmol) is dissolved in 10 ml of methanol. After addition of 10% palladium on carbon (45 mg) the mixture is hydrogenated at room temperature for 20h. Then the mixture is filtrated over celite. Evaporation gave 240 mg (99%) of a colorless oil.
MS (ESI): 158.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.25 (m, 1H), 4.12 (m, 1H), 2.9-3.1 (m, 3H), 2.78 (m, 1H), 1.85-2.40 (m, 3H), 1.52 (s, 3H), 1.38 (s, 3H).

(5) **1-(2,2-Dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-5-yl)-propan-2-ol (30)(single enantiomer, absolute configuration of dioxol unknown)**

34 (90 mg, 0.57 mmol), (R)-(+)-propylenoxide (166 mg, 2.8 mmol), and triethylamine (160 ul, 1.1 mmol) are dissolved in 2 ml of ethanol and stirred at room temperature for 4h. The reaction mixture is diluted with 20 ml of ethyl acetate, washed subsequently with 1N NaOH and brine, dried over sodium sulphate and evaporated. The crude product, 100 mg of a yellow oil, is purified by Flash-chromatography (silica gel, dichloromethane / methanol / ammonia 95:5:0.5).
Yield: 70 mg (57%). MS (ESI): 216.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.03-4.28 (m, 2H), 3.9 (m, 1H), 2.2-3.08 (m, 6H), 1.36-2.13 (m, 3H), 1.51 (s, 3H), 1.38 (s, 3H), 1.12-1.22 (dd, 3H).

Synthesis of (R)-1-(2,2,7-trimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-5-yl)-propan-2-ol (35) (reaction scheme 5):



(1) **Trifluoro-methanesulfonic acid 1-benzyl-3-(R,S)-methyl-1,2,3,6-tetrahydro-pyridin-4-yl ester (36)**

1M lithium-bis-(trimethylsilyl)-amid solution in THF (540 ul, 0.54mmol) is diluted with 1 ml of THF and cooled to -78°C. A solution of 1-benzyl-3-methyl-4-piperidone (100 mg, 0.49 mmol) in 0.5 ml THF is added via syringewithin 5 min. After stirring for 2 h at this temperature, a solution of N-phenyl-trifluoromethansulfonimid (188 mg, 0.52 mmol) in 1 ml of THF is added within 10 min. The beige suspension is stirred for another 4h at 0°C. The yellow solution is quenched with 1 ml of saturated ammonium chloride solution, diluted with ice-cold water and three times extracted with ethyl acetate. The organic layers are washed with brine, dried over sodium sulphate and evaporated. The crude product, 311 mg of a yellow oil, is purified by Flash-chromatography (silica gel, cyclohexane / ethyl acetate 4:1).
Yield: 127 mg (77%) of a colorless oil. MS (ESI): 336 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.22 – 7.36 (m, 5H), 5.69 (dd, 1H), 3.54-3.65 (m, 2H), 3.05 (br s, 2H), 2.75 (m, 1 H), 2.59 (m, 1H), 2.32 (m, 1H), 1.06 (d, 3H).

(2) **1-Benzyl-3-(R,S)-methyl-1,2,3,6-tetrahydro-pyridine (37)**

36 from above (100 mg, 0.3 mmol), palladium-(II)-acetate (1.34 mg, 6 umol), triphenylphosphin (3.1 mg, 12 umol) and triethylamine (125 ul, 0.9 mmol) are dissolved in 1 ml of DMF. After addition of formic acid (22.5 ul, 0.6 mmol) the mixture is stirred for 1h at 60°C. The reaction mixture is diluted with ethyl acetate, washed subsequently with 1N NaOH and brine, dried over sodium sulphate and evaporated. The crude product, 78 mg of a yellow oil, is purified by Flash-chromatography (silica gel, cyclohexane / ethyl acetate 3:1).
Yield: 42 mg (75%) of a yellow oil. MS (ESI): 188.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.23-7.41 (m, 5H), 5.62 (s, 2H), 3.63 (br s, 2H), 3.12 (d, 1H), 2.83 (m, 2H), 2.48 (m, 1H), 2.02 (br s, 1H), 0.96 (d, 3H).

(3) **(3RS,4SR,5RS)-1-Benzyl-5-methyl-piperidine-3,4-diol (racemic) (38)**

37 (570 mg, 3 mmol) is dissolved in 10 ml of a 1:1 mixture of water and acetone. After addition of N-methyl-morpholine-N-oxide (529 mg, 4.5 mmol), a 2.5% solution of osmium tetroxide in tert. Butanol (527 ul, 52 umol) is added. The mixture is stirred at room temperature for 24h. Then 10 ml of a saturated sodium bisulfite solution is added. After 15 min stirring at room temperature, the reaction mixture is extracted with ethyl acetate. The

organic layers are washed subsequently with 1N NaOH and brine, dried over sodium sulphate and evaporated. The crude product, 460 mg of a dark brown oil, is purified by Flash-chromatography (silica gel, dichloromethane / methanol / ammonia 95:5:0.5).
Yield: 290 mg (43%) of the cis diol, trans to the methyl group and 20mg (3%) of the all-cis derivative. MS (ESI): 222 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.17-7.32 (m, 5H), 4.21 (d, 1H), 4.04 (br d, 1H), 3.58 (m, 1H), 3.41 (dd, 2H), 3.02 (m, 1H), 2.62 (m, 1H), 2.56 (br d, 1H), 2.12 (br d, 1H), 1.69-1.88 (m, 2H), 0.86 (d, 3H).

(4) (3aRS,7RS,7aSR)-5-Benzyl-2,2,7-trimethyl-hexahydro-[1,3]dioxolo[4,5-c]pyridine (racemic) (39)

38 from above (290 mg, 1.3 mmol) is dissolved in 4 ml of dichloromethane. After portionwise addition of 2,2-dimethoxypropane (1.6 ml, 13 mmol) and p-toluene sulfonic acid (300 mg, 1.6 mmol) the mixture is stirred at room temperature for 16h. Then the mixture is diluted with dichloromethane, washed subsequently with 1N NaOH and brine, dried over sodium sulphate and evaporated. The crude product, 333 mg of a yellow oil, is purified by Flash-chromatography (silica gel, cyclohexane / ethyl acetate 3:1).
Yield: 303 mg (89%) MS (ESI): 262.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.20-7.40 (m, 5H), 4.19 (br s, 1H), 3.69 (br s, 1H), 3.43-3.63 (m, 2H), 2.89 (m, 1H), 2.53 (m, 2H), 2.02 (m, 1H), 1.88 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.00 (d, 3H).

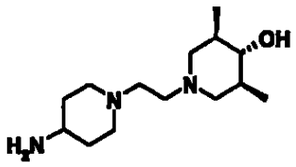
(5) (3aRS,7RS,7aSR)-5-Benzyl-2,2,7-trimethyl-hexahydro-[1,3]dioxolo[4,5-c]pyridine (racemic) (40)

39 from above (250 mg, 0.98 mmol) is dissolved in 5 ml of isopropanol. After addition of 10% palladium on carbon (25 mg) the mixture is hydrogenated at room temperature for 16h. Then the mixture is filtrated over celite. Evaporation gave 170 mg (100%) of a colorless oil.
MS (ESI): 172.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.05 (m, 1H), 3.67 (dd, 1H), 3.39 (d, 1H), 2.98 (m, 2H), 2.21 (t, 1H), 2.05 (m, 1H), 1.73 (m, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 0.98 (d, 3H).

(6) 1-(2,2,7-Trimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-5-yl)-propan-2-ol (35) (mixture of diastereomers)

40 (175 mg, 1 mmol), (R)-(+)-propylenoxide (297 mg, 5.1 mmol), and triethylamine (285 ul, 2 mmol) are dissolved in 3 ml of ethanol and stirred at room temperature for 5h. After evaporation the residue is dissolved in ethyl acetate, washed subsequently with 1N NaOH and brine, dried over sodium sulphate and evaporated. The crude product, 214 mg of a yellow oil, is purified by Flash-chromatography (silica gel, dichloromethane / methanol / ammonia 95:5:0.5).
Yield: 140 mg (60%). MS (ESI): 172.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.05 (m, 1H), 3.67 (dd, 1H), 3.39 (d, 1H), 2.98 (m, 2H), 2.21 (t, 1H), 2.05 (m, 1H), 1.73 (m, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 0.96 (d, 3H).

Synthesis of (3R,4R,5S)-1-[2-(4-Amino-piperidin-1-yl)-ethyl]-3,5-dimethyl-piperidin-4-ol tri-hydrochloride (41) (reaction scheme 6):



(1) N'-[1-Benzyl-3-methyl-piperidin-(4E)-ylidene]-N,N-dimethyl-hydrazine (42)

N,N-dimethylhydrazine (3 ml, 39.3 mmol) and 1-benzyl-3-methyl-piperidin-4-one (4 g, 19.7 mmol) are dissolved in 50 ml of ethanol and refluxed for 18 hours. The reaction mixture is evaporated under reduced pressure and dried at high vacuum.
Yield: 4.8g g of a pale oil (99%). MS (ESI): 246 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.29 (m, 4H), 7.23 (m, 1H), 3.48 (m, 2H), 2.8 (m, 1H), 2.65 (m, 1H), 2.35 – 2.55 (m, 2H), 2.29 (s, 6H), 2.25 (m, 1H), 1.9 – 2.1 (m, 1H), 1.00 (d, 3H).

(2) N'-(1-Benzyl-3,5-dimethyl-piperidin-4-ylidene)-N,N-dimethyl-hydrazine (43)

Diisopropylamine (3.3 ml, 23.5 mmol) is dissolved in 20 ml of THF and cooled to -5°C. A 1.6M solution of n-butyllithium in THF (14.7 ml, 23.5 mmol) is added dropwise within 10 min. After additional 10 min at -5°C, a solution of 42 (4.8 g, 19.6 mmol) in 30 ml of THF is added within 20 min (the color of the reaction mixture changed to red). Now, the solution is cooled to -78 C. Methyliodide (1.33 ml, 21.5 mmol) is added dropwise within 15 min and the mixture is allowed to warm to room temperature over night. Dichloromethane is added and the

solution is washed with water. Evaporation gave 5 g of a colorless oil, which is further purified by flash-chromatography (silicagel, ethyl acetate / hexanes 1:1)
Yield: 1.7g g of a white solid (33%). MS (ESI): 280 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.33 (m, 4H), 7.22 (m, 1H), 3.48 (m, 2H), 3.37 (m, 1H), 2.88 (m, 1H), 2.59 (m, 1H), 2.43 (m, 1H), 2.43 (m, 1H), 2.29 (s, 6H), 2.15 (m, 1H), 2.0 (m, 1H), 1.23 (d, 6H).

(3) 1-Benzyl-3,5-dimethyl-piperidin-4-one (44)

43 (1.7 g, 6.5 mmol) is dissolved in a 1.25M solution of HCl in methanol (20 ml, 25 mmol) and refluxed for 1.5 h The reaction mixture is evaporated under reduced pressure and dried at high vacuum. The residue (1.7 g of a colorless oil) is dissolved in ethyl acetate and treated with 5M NaOH. The organic layers are evaporated under reduced pressure.
Yield: 1.4g g of a colorless oil (84%). MS (ESI): 218 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.3 (m, 4H), 7.25 (m, 1H), 3.58 (m, 2H), 3.07 (m, 2H), 2.68 (m, 2H), 1.97 (dd, 2H), 0.82 (d, 6H).

(4) 1-Benzyl-3,5-dimethyl-piperidin-4-ol (45)

Sodiumboronhydride (121 mg, 3.2 mmol) is added to a solution of 44 (1.4 g, 6.4 mmol) in 15 ml of methanol and the mixture is stirred at room temperature for 30 min. The mixture is evaporated, and the residue is dissolved in ethyl acetate and washed with water.
Yield: 1.4g g of a colorless oil (99%). MS (ESI): 220 $[M+H]^+$.

(5) Acetic acid (3S,4R,5R)-1-benzyl-3,5-dimethyl-piperidin-4-yl ester (46)

DMAP (40 mg, 0.3 mmol) is added to a solution of 45 (1.4 g, 6.4 mmol) in 10 ml of pyridine. After addition of acetic anhydride (0.9 ml, 9.5 mmol) the mixture is stirred at 110°C for 2h. The mixture is evaporated, and the residue is dissolved in dichloromethane and and washed with water. Evaporation gave 1.6 g of a colorless oil, which is further purified by flash-chromatography (silicagel, ethyl acetate / hexanes 1:9)
Yield: 0.7 g of a colorless oil (42%, fraction 1). MS (ESI): 262 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.2 – 7.3 (m, 5H), 4.18 (dd, 1H), 3.42 (s, 2H), 2. 8 (m, 2H), 2.05 (s, 3H), 1.7 – 1.8 (m, 4H), 0.72 (d, 6H).

(6) Acetic acid (3R,4R,5S)-3,5-dimethyl-piperidin-4-yl ester (47)

Palladium hydroxide on carbon (20%, 300 mg) is placed into a flask filled with argon and carefully covered with 25 ml of methanol. A solution of 46 (0.7 g, 2.7 mmol) in methanol is added and the mixture is hydrogenated at room temperature for 15h. After filtration over celite, the filtrate is evaporated and dried under high vacuum.
Yield: 0.41 g of a colorless oil (89%). MS (ESI): 172 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.22 (dd, 1H), 2. 8 (dd, 2H), 2.15 (dd, 2H), 2.05 (s, 3H), 1.5 (m, 2H), 0.7 (d, 6H).

(7) Acetic acid (3S,4R,5R)-1-[2-(4-tert-butoxycarbonylamino-piperidin-1-yl)-ethyl]-3,5-dimethyl-piperidin-4-y ester (48)

47 (2.3 g, 13.4 mmol) is dissolved in 5 ml of propionitril and after addition of 8 (3.3 g, 13.4 mmol), cyanomethyl-trimethyl-phosphonium iodide (4.4g, 33.6 mmol) and N-ethyldiisopropylamine (11.5 ml, 67.1 mmol) the mixture is refluxed for 24 h (TLC control). Then the mixture is evaporated under reduced pressure. The residue is diluted with ethyl acetate, washed 10% K2CO3 - and NaCl-solution, and dried over Na2SO4.
Yield: 3.3 g of a brown oil (62%). MS (ESI): 398 $[M+H]^+$.

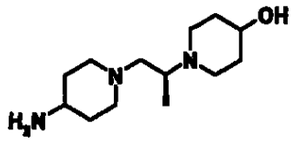
(8) {1-[2-((3S,4R,5R)-4-Hydroxy-3,5-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (49)

48 (3.3 g, 8.3 mmol) is dissolved in 100 ml of methanol and after addition of NaOMe powder (2.2g, 41.5 mmol) the mixture is refluxed for 6 h (TLC control). Then the mixture is evaporated under reduced pressure. The residue is diluted with ethyl acetate, washed with water, and dried over Na2SO4. Evaporation gave 3.1 g of a brown oil. The crude product is purified by recrystallization from ether.
Yield: 800 mg of a colorless solid (27%). MS (ESI): 356 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.7 (br d, 1H), 4.4 (d, 1H), 3.15 (br m, 1H), 2.75 (m, 4H), 2.4 (m, 1H), 2.3 (m, 4H), 1.9 (m, 2H), 1.3 – 1.7 (m, 8H), 1.38 (s, 9H), 0.85 (d, 6H).

(9) 3R,4R,5S)-1-[2-(4-Amino-piperidin-1-yl)-ethyl]-3,5-dimethyl-piperidin-4-ol tri-hydrochloride (41)

49 is dissolved in a 4M solution of HCl in dioxane (20 ml) and stirred for 4 h (TLC control) at room temperature. Then the mixture is cooled down to 0 C and filtrated. The residue is washed with ether. Evaporation gave 510 mg (89%) of grey crystals.
MS (ESI): 256 $[M+H]^+$.

Synthesis of 1-[(S)-2-(4-Amino-piperidin-1-yl)-1-methyl-ethyl]-piperidin-4-ol tri-hydrochloride (50) (reaction scheme 7):



(1) 2,2-Dimethyl-propionic acid 1-benzyl-piperidin-4-yl ester (51)

A solution of 1-benzyl-piperidin-4-ol (25 g, 130.7 mmol) and triethylamine (36.1 ml, 261.4 mmol) in 250 ml of THF is treated with 2,2-dimethyl-propionyl chloride (32.2 ml, 261.4 mmol). The suspension is heated under reflux over night. The solvent is evaporated, the residue taken up in DCM and washed with saturated sodium bicarbonate solution and brine. Drying and evaporation gave an orange oil.
Yield: 38.3 g (100% crude). MS (ESI): 276 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.31 (m, 4H), 7.25 (m, 1H), 4.79 (m, 1H), 3.5 (s, 2H), 2.61 (m, 2H), 2.32 (m, 2H), 1.86 (m, 2H), 1.69 (m, 2H), 1.18 (s, 9H).

(2) 2,2-Dimethyl-propionic acid piperidin-4-yl ester (52)

A solution of piperidine 51 (35.99 g, 130.7 mmol) in methanol is hydrogenated with Pd/C in the presence of one equivalent of HCl (104.5 ml, 130.7 mmol, 1.25M in MeOH). After filtration and evaporation, the crude is taken up in ether and washed with 1N-NaOH and brine. Drying, evaporation and distillation (0.08 mbar, 75-80C) gave a colourless oil. Yield: 17.98 g (74%).
MS (ESI): 186 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 9.22 (br s, 1H), 4.89 (m, 1H), 3.08 (m, 4H), 1.99 (m, 2H), 1.78 (m, 2H), 1.15 (s, 9H).

(3) 2,2-Dimethyl-propionic acid 1-((R)-2-hydroxy-propyl)-piperidin-4-yl ester (53)

A solution of piperidine 52 (2 g, 10.8 mmol) and (R)-2-Methyl-oxirane (3.78 ml, 54 mmol) in 2 ml of ethanol is stirred for 24 hours in a closed flask. The solvent is evaporated and the residue distilled in a Kugelrohr apparatus (0.08 mbar, 75-90C).
Yield: 2.58 g (98%).
MS (ESI): 244.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.65 (m, 1H), 4.1 (br s, 1H), 3.72 (m, 1H), 2.55 (m, 2H), 2.31 (m, 2H), 2.23 (m, 1H), 2.14 (m, 1H), 1.75 (m, 2H), 1.55 (m, 2H), 1.14 (s, 9H), 1.03 (d, 3H), $[\alpha]_D$ = -23.1 (c=1 in MeOH)

(4) 2,2-Dimethyl-propionic acid 1-[(S)-2-(4-tert-butoxycarbonylamino-piperidin-1-yl)-1-methyl-ethyl]-piperidin-4-yl ester (54)

A solution of alcohol 53 (1.26 g, 5.16 mmol) and triethylamine (1.43 ml, 10.32 mmol) in 80 ml of DCM is cooled to -78C. Triflic anhydride (0.85 ml, 5.16 mmol) is slowly added and stirring continued for 1 hour. The mixture is then allowed to warm up to 0C and cooled back to -78C after 15 minutes. A solution of piperidin-4-yl-carbamic acid tert-butyl ester, 3, (1.03 g, 5.16 mmol) in 40 ml of DCM is slowly added at -78C. After complete addition, the cooling bath is removed and the dark solution is allowed to warm up to room temperature. The mixture is washed twice with water, dried over sodium sulphate, filtered and evaporated. The crude is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (1%).
Yield: 1.7 g (77%).
MS (ESI): 426.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.74 (m, 1H), 4.43 (m, 1H), 3.43 (br m, 1H), 2.89 (m, 1H), 1.97-2.82 (m, 11H), 1.87 (m, 4H), 1.64 (m, 2H), 1.43 (s, 9H), 1.38 (m, 1H), 1.19 (s, 9H), 1.0 (d, 3H). $[\alpha]_D$ = -9.3 (c=1 in MeOH)

(5) {1-[(S)-2-(4-Hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (55)

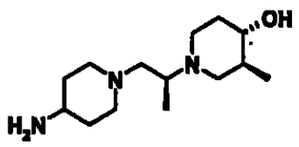
Ester 54 from above (1.7 g, 3.52 mmol) is treated with NaOMe (0.5M in methanol, 21 ml, 10.5 mmol) and heated under reflux for 24 hours. The solvent is then evaporated, the residue taken up in DCM and extracted with 1N-NaOH and brine. After drying and evaporation the crued is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 1% to 3%) to give a white powder.

Yield: 0.77 g (56%). MS (ESI): 342.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.43 (m, 1H), 3.64 (m, 1H), 3.43 (m, 1H), 2.88 (m, 1H), 2.75 (m, 4H), 1.8-2.45 (m, 10H), 1.3-1.65 (m, 5H), 1.44 (s, 9H), 0.99 (d, 3H). $[\alpha]_D$ = -15.3 (c=1 in MeOH).

(6) 1-[(S)-2-(4-Amino-piperidin-1-yl)-1-methyl-ethyl]-piperidin-4-ol tri-hydrochloride (50)

It is prepared by BOC-cleavage of tert-butyl ester 55 (0.666 g, 1.95 mmol) with 4M-HCl in dioxane (2.93 ml, 11.72 mmol) as described for amine 7.
Yield: 0.64 g (93%). MS (ESI): 242.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 10.5-10.85 (br m, 2H), 8.3-8.8 (br m, 3H), 2.75-4.15 (br m, 15H), 1.6-2.3 (br m, 7H), 1.39 (d, 3H). $[\alpha]_D$ = +13.2 (c=1 in MeOH)

Synthesis of (3S,4S)-1-[(S)-2-(4-Amino-piperidin-1-yl)-1-methyl-ethyl]-3-methyl-piperidin-4-ol tri-hydrochloride (56) (reaction scheme 7):



(1) 2,2-Dimethyl-propionic acid (3S,4S)-1-((R)-2-hydroxy-propyl)-3-methyl-piperidin-4-yl ester (57)

A solution of piperidine 17 (2 g, 10.8 mmol) and (R)-2-Methyl-oxirane (3.78 ml, 54 mmol) in 2 ml of ethanol is stirred for 24 hours in a closed flask. The solvent is evaporated and the residue distilled in a Kugelrohr apparatus (0.08 mbar, 75-90C).
Yield: 2.58 g (98%). MS (ESI): 258.2 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 4.39 (td, 1H), 3.82 (m, 1H), 2.95 (m, 1H), 2.76 (m, 1H), 2.42 (td, 1H), 2.17-2.33 (m, 2H), 1.96 (m, 1H), 1.75-1.9 (m, 2H), 1.62 (m, 1H), 1.2 (s, 9H), 1.13 (d, 3H), 0.89 (d, 3H). $[\alpha]_D$ = -23.1 (c=1 in MeOH)

(2) 2,2-Dimethyl-propionic acid (3S,4S)-1-[(S)-2-(4-tert-butoxycarbonylamino-piperidin-1-yl)-1-methyl-ethyl]-3-methyl-piperidin-4-yl ester (58)

A solution of alcohol 57 (1.26 g, 5.16 mmol) and triethylamine (1.43 ml, 10.32 mmol) in 80 ml of DCM is cooled to -78C. Triflic anhydride (0.85 ml, 5.16 mmol) is slowly added and stirring continued for 1 hour. The mixture is then allowed to warm up to 0C and cooled back to -78C after 15 minutes. A solution of piperidin-4-yl-carbamic acid tert-butyl ester, 3, (1.03 g, 5.16 mmol) in 40 ml of DCM is slowly added at -78C. After complete addition, the cooling bath is removed and the dark solution is allowed to warm up to room temperature. The mixture is washed twice with water, dried over sodium sulphate, filtered and evaporated. The crude is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (1%).

Yield: 1.7 g (77%). MS (ESI): 440.3 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 4.3 (td, 1H), 3.34 (m, 1H), 3.01 (m, 1H), 2.78-2.91 (m, 4H), 2.52 (dd, 1H), 2.42 (td, 1H), 2.02-2.3 (m, 4H), 1.94 (m, 1H), 1.84 (m, 3H), 1.5 (m, 3H), 1.45 (s, 9H), 1.21 (s, 9H), 1.04 (d, 3H), 0.9 (d, 3H). $[\alpha]_D$ = -9.3 (c=1 in MeOH)

(3) **{1-[(S)-2-((3S,4S)-4-Hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (59)**

Ester 58 from above (1.7 g, 3.52 mmol) is treated with NaOMe (0.5M in methanol, 21 ml, 10.5 mmol) and heated under reflux for 24 hours. The solvent is then evaporated, the residue taken up in DCM and extracted with 1N-NaOH and brine. After drying and evaporation the crued is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 1% to 3%) to give a white powder.

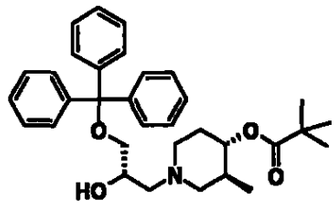
Yield: 0.77 g (56%). MS (ESI): 356.3 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 4.86 (s, 1H), 3.32 (m, 1H), 2.94-3.06 (m, 2H), 2.72-2.87 (m, 3H), 2.49 (dd, 1H), 2.34 (td, 1H), 2.14-2.28 (m, 2H), 1.97-2.1 (m, 2H), 1.75-1.93 (m, 3H), 1.53 (m, 4H), 1.44 (s, 9H), 1.04 (d, 3H), 0.97 (d, 3H). $[\alpha]_D$ = -15.3 (c=1 in MeOH)

(4) **(3S,4S)-1-[(S)-2-(4-Amino-piperidin-1-yl)-1-methyl-ethyl]-3-methyl-piperidin-4-ol tri-hydrochloride (56)**

It is prepared by BOC-cleavage of tert-butyl ester 59 (0.666 g, 1.95 mmol) with 4M-HCl in dioxane (2.93 ml, 11.72 mmol) as described for amine 7.

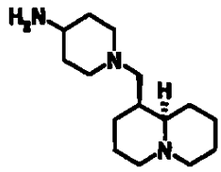
Yield: 0.64 g (93%). MS (ESI): 256.2 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 4.25 (br m, 1H), 4.03 (br m, 3H), 3.05-3.9 (m, 9H), 1.95-2.55 (m, 7H), 1.54 (d, 3H), 1.1 (d, 3H). $[\alpha]_D$ = +13.2 (c=1 in MeOH)

Synthesis 2,2-Dimethyl-propionic acid (3S,4S)-1-((S)-2-hydroxy-3-trityloxy-propyl)-3-methyl-piperidin-4-yl ester (60):



(S)-2-Trityloxymethyl-oxirane (636 mg, 2 mmol) and 2,2-dimethyl-propionic acid (3S,4S)-3-methyl-piperidin-4-yl ester (17, 400 mg, 2 mmol) are dissolved in 7 ml of ethanol and stirred at room temperature for 23h. The white suspension is heated to 40°C and stirred for additional 2h. The reaction mixture is evaporated under reduced pressure and the crude product is purified by Flash-chromatography. (silica gel, 20 % ethyl acetate in cyclohexane). Yield: 681 mg (66%) of a white foam. MS (ESI): 516.4 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.4 (d, 6H), 7.31 (dd, 6H), 7.23 (dd, 3H), 4.62 (d, 1H), 4.22 (m, 1H), 3.74 (m, 1H), 2.95 (d, 2H), 2.72 (m, 2H), 2.22 – 2.41 (m, 2H), 2.07 (m, 1H), 1.58 – 1.84 (m, 3H), 1.14 (s, 9H), 0.76 (d, 3H).

Synthesis of (1-[(1S,9aR)-1-(Octahydro-quinolizin-1-yl)methyl]-piperidin-4-ylamine tri-hydrochloride (61) (reaction scheme 8):



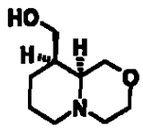
(1) **(1-[(1S,9aR)-1-(Octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl)-carbamic acid tert-butyl ester (62)**

3 (3 g, 15 mmol) is dissolved in 150ml of propionitril. Ethyldiisopropylamine (10.2 ml, 60 mmol), (-)-lupinine (2.5 g, 15 mmol) and cyanomethyl-trimethyl-phosphonium iodide (Zaragoza reagent, 7.3 g, 30 mmol) are added. The reaction mixture is heated to 120°C and stirred for 22 hours. Then the mixture is evaporated under reduced pressure. The residue is dissolved with ethyl acetate, washed 10% K2CO3 - and NaCl-solution, and dried over Na2SO4. Evaporation gave 5.7 g of a brown oil. The crude product is purified by Flash-chromatography (ethyl acetate, then methanol /ethyl acetate (4:6), silicagel).
Yield: 4.3 g (61.7%) of a brown oil. MS (ESI): 352 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 6.7 (br d, 1H), 3.2 (m, 1H), 2.7 – 2.75 (m, 4H), 2.4 (dd, 1H), 2.2 (dd, 1H), 1.38 (s, 9H), 1.15 - 2.0 (m, 20H).

(2) **1-[(1S,9aR)-1-(Octahydro-quinolizin-1-yl)methyl]-piperidin-4-ylamine trihydrochloride (61)**

The ester 62 (3.8 g, 10.8 mmol) is dissolved in 15 ml of dioxane and after addition of 70 ml of a 4M solution of HCl in dn of HCl in dioxan the mixture is stirred for 4 hours at RT. The product is filtered off and is used in the next step without further purification.
Yield: 3.9g (100%). MS (ESI): 252 $[M+H]^+$.

Synthesis of (9R,9aS)-1-(Octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)-methanol (racemate) (63) (reaction scheme 9):



(1) **4-(3-Bromo-propyl)-morpholine-3,5-dione (64)**

A pale yellow suspension of morpholine-3,5-dione (1.2 g, 10 mmol), of 1,3-dibromopropane (3.4 ml, 33 mmol), and potassium carbonate (2.7 g, 19 mmol) in 23 ml of 2-butanone is refluxed under an argon athmosphere for 22 hours. After cooling, the suspension is concentrated on a rotary evaporator, poured into ice/water, and extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried over anhydrous sodium sulphate, and evaporated. The residual yellow oil (2.06 g) is purified by chromatography (Biotage 40Mi, i= 15 cm, cyclohexane/ethyl acetate 3:1).

Yield: 1.24 g (52.5%) of a colorless oil. MS (EI): 235 $[M]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.37 (s, 4H), 3.95 (t, 2H), 3.39 (t, 2H), 2.18 (m, 2H).

(2) **4-Oxo-1,3,4,6,7,8-hexahydro-pyrido[2,1-c][1,4]oxazine-9-carboxylic acid ethyl ester (65)**

To an ice-cold suspension of sodium hydride (150 mg, 60% in mineral oil3.75 mmol) in 25 ml of anhydrous THF under argon is added a solution of triethyl phosphonoacetate (0.31 ml, 1.5 mmol) in 6 ml of anhydrous THF. The suspension is stirred at RT for 2 hrs, then 64 (354 mg, 1.5) in 6 ml of THF is added, and the resulting mixture is refluxed for 10 hours. After cooling, the suspension is concentrated on a rotary evaporator, poured onto ice/sat. aqueous ammonium chloride solution, and extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried over anhydrous sodium sulphate, and evaporated. The residual yellow oil (339 mg) is purified by chromatography (Biotage 12Mi, l= 15.5 cm, cyclohexane/ethyl acetate 3:1).

Yield: 60.3 mg (17.8%) of a colorless oil. MS (ESI): 226 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 4.94 (s, 2H), 4.27 (s, 2H), 4.20 (q, 2H), 3.75 (dd, 2H), 2.45 (m, 2H), 1.88 (m, 2H),1.30 (t, 3H)

(3) **(9RS,9aSR)-4-Oxo-octahydro-pyrido[2,1-c][1,4]oxazine-9-carboxylic acid ethyl ester (racemate) (66)**

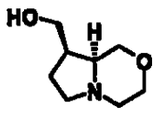
A solution of 65 (225 mg, 1.0 mmol) in 5 ml of acetic acid is hydrogenated over 225 mg of platinum dioxide at RT and normal pressure for 18 hours. Another 225 mg of platinum dioxide is added and hydrogenation continued for 24 hours. The black suspension is diluted with 10 ml of DCM and filtered through a pad of celite. The filtrate is evaporated to give 268 mg of a yellow oil which is purified by chromatography (Biotage 12Si, l= 7.5 cm, ethyl acetate/ethanol 9:1).

Yield: 144 mg (63.3%) of a yellow oil. MS (ESI): 228 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.45 (m, 1H), 4.00 (m, 2H), 3.9 – 3.75 (m, 4H), 3.60 (m, 1H), 2.65 (m, 1H), 2.55 (m, 1H), 1.90 (m, 2H), 1.75 (m, 1H), 1.45 (m, 1H), 1.16 (t, 3H).

(4) **(9RS,9aSR)-1-(Octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)-methanol (racemate) (63)**

To a solution of 66 (114 mg, 0.5 mmol) in 5 ml of anhydrous THF is added LAH (40 mg, 1.0 mmol) and the mixture refluxed for 9 hours. The mixture is cooled to 0°C and treated successively with 0.04 ml of water, 3N aqueous sodium hydroxide (0.04 ml, 0.12), and 0.12 ml of water. The mixture is stirred for 15 min. and then extracted three times with DCM. The combined organic phases are dried over anhydrous sodium sulphate and evaporated under educed pressure. The residual pale yellow oil (75 mg) is purified by chromatography (Biotage 12SI, I= 7.5 cm, DCM/MeOH/conc. Ammonia 95:4.5:0.5).
Yield: 35.1 mg (41.0%) of a pale yellow oil. MS (ESI): 172 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.30 (br s, 1H), 3.65-3.55 (m, 4H), 3.50 – 3.35 (m, 2H), 2.70 (br d, 1H), 2.55 (br d, 1H), 2.10-1.95 (m, 2H), 1.85 - 1.60 (m, 2H), 1.60-1.50 (m, 2H), 1.35-1.20 (m, 2H).

Synthesis of (8R,8aS)-1-(hexahydro-pyrrolo[2,1-c][1,4]oxazin-8-yl)-methanol (racemate) (67) (reaction scheme 10):



(1) 4-Oxo-3,4,6,7-tetrahydro-1H-pyrrolo[2,1-c][1,4]oxazine-8-carboxylic acid ethyl ester (68)

To a suspension of sodium hydride (480 mg, 60% in mineral oil, 12 mmol) in 10 ml of anhydrous THF is added morpholine-3,5-dione (1.2 g, 10 mmol) in 20 ml of THF under an argon athmosphere. After 10 min., 1-carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (Fuchs' reagent, 6.8 g, 11 mmol)) in 20 ml of THF are added and the mixture is refluxed for 21 hours. After cooling, the suspension is concentrated on a rotary evaporator, poured onto ice/sat. sodium bicarbonate solution, and extracted three times with ether. The combined organic phases are washed with brine, dried over anhydrous sodium sulphate, and evaporated. The residual yellow oil (3.04 g) is purified by chromatography (Silica gel 60, 0.063-0.2 mesh, cyclohexane/ethyl acetate 1:1).
Yield: 1.08 g (51.2%) of a colorless solid. MS (EI): 211 $[M]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.77 (s, 2H), 4.17 (s, 2H), 4.11 (q, 2H), 3.82 (m, 2H), 2.70 (m, 2H), 1.22 (t, 3H).

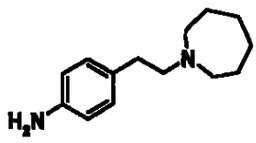
(2) (8RS,8aSR)-4-Oxo-hexahydro-pyrrolo[2,1-c][1,4]oxazine-8-carboxylic acid ethyl ester (racemate) (69)

A solution of 68 (1.056 g, 5.0 mmol) in 25 ml of acetic acid is hydrogenated over 1.056 g of platinum dioxide at RT and normal pressure for 18 hours. The black suspension is diluted with 20 ml of DCM and filtered through a pad of celite.The filtrate is evaporated to give 1.09 g of a yellow oil which is purified by chromatography (Silica gel 60, 0.063-0.2 mesh, ethyl acetate/ethanol 9:1).
Yield: 809 mg (75.7%) of a yellow oil. MS (ESI): 214 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.15-3.80 (m, 6H), 3.70-3.05 (m, 4H), 2.70 – 1.90 (m, 2H), 1.18 (t, 3H).

(3) (8RS,8aSR)-1-(Hexahydro-pyrrolo[2,1-c][1,4]oxazin-8-yl)-methanol (racemate) (67)

To a solution of 69 (1.1 g, 5.0 mmol)in 50 ml of anhydrous THF are added LAH (400 mg, 10 mmol) and the mixture refluxed for 18 hours. The mixture is cooled to 0°C and treated successively with 0.4 ml of water, 0.4 ml of 3N aq. sodium hydroxide, and 1.2 ml of water. The mixture is stirred for 15 min. and then extracred three times with DCM. The combined organic phases are dried over anhydrous sodium sulphate and evaporated. The residual yellow oil (880 mg) is purified by chromatography (Silica gel 60, 0.063-0.2 mesh, DCM/MeOH/conc. ammonia 90:9:1).
Yield: 552 mg (70.2%) of a pink oil. MS (ESI): 158 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.42 (br s, 1H), 3.85 (m, 1H), 3.65 (m, 1H), 3.35 (m, 2H), 3.15 (m, 1H), 2.95 (m, 1H), 2.85 (m, 1H), 2.15-1.90 (m, 5H), 1.75 (m, 1H), 1.20 (m, 1H).

<u>Synthesis of 4-(2-Azepan-1-yl-ethyl)-phenylamine di-hydrochloride (70):</u>



(1) 1-[2-(4-Nitro-phenyl)-ethyl]-azepane (71)

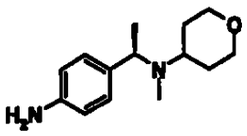
1-(2-Bromo-ethyl)-4-nitro-benzene (10 g, 43.47 mmol) is added under argon to a mixture of azepane (4.9 ml, 43.47 mmol) and potassium carbonate (6 g, 43.47 mmol) in 100 ml of

DMF. After stirring over night at room temperature, the mixture is filtered and evaporated under high vacuum. The residue is dissolved in ethyl acetate, washed with water and brine and dried over sodium sulfate. Evaporation gave 9.1 g (84%) of a yellow oil.
MS (ESI): 247.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.15 (d, 2H), 7.55 (d, 2H), 2.87 (t, 2H), 2.73 (t, 2H), 2.65 (t, 4 H), 1.5 – 1.8 (m, 8H).

(2) 4-(2-Azepan-1-yl-ethyl)-phenylamine di-hydrochloride (70)

Compound 71 (9.1 g, 36.65 mmol) is hydrogenated for 3h at room temperature with palladium on carbon in 150 ml of ethanol and 18.3 ml of 4M aqueous hydrochloric acid. The mixture is filtered over celite and evaporated.
Yield: 10.7 g (100%) of a beige solid. MS (ESI): 219 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 10.85 (br, 1H), 9.8 (br, 3H), 7.3 (m, 2H), 7.2 (m, 2H), 3.42 (m, 2H), 3.25 (m, 2H), 3.18 (m, 2 H), 3.08 (m, 2H), 1.85 (m, 4H), 1.68 (m, 2H), 1.58 (m, 2H).

Synthesis of [(R)-1-(4-Amino-phenyl)-ethyl]-methyl-(tetrahydro-pyran-4-yl)-amine di-hydrochloride (72) (reaction scheme 11):



(1) Methyl-[(R)-1-(4-nitro-phenyl)-ethyl]-(tetrahydro-pyran-4-yl)-amine (73)

(R)-α-Methyl-4-nitro-benzylammonium hydrochloride (Aldrich, 3 g, 15 mmol), tetrahydropyridon (1.5 g, 15 mmol), pyridine (1.2 ml, 15 mmol) are dissolved in 100 ml DCE. Sodium triacetoxyborohydride (4 g, 19 mmol, 95%) is added under stirring at room temperature; after 18 hours reaction time formaldehyde (2.4 ml, 30% in water) is added followed by sodium triacetoxyborohydride (3 g, 14 mmol, 95%) and the mixture is again stirred for 18 hours at room temperature. After addition of 2m HCl the product is isolated by distribution between aqueous ammonia and EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product (3.2 g, 82 %) is used without further purification.
MS (ESI): 265 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.20 (d, 2H), 7.55 (d, 2H), 4.0 (br m, 2H), 3.95 (br m, 1H), 3.3 (br m, 2H), 2.7 (br m, 1H), 2.20 (s, 3H), 1.7 (br m, 4H), 1.40 (d, 3H)

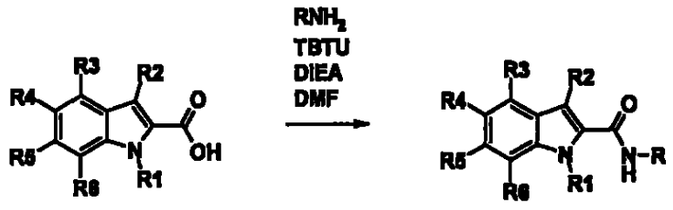
(2) [(R)-1-(4-Amino-phenyl)-ethyl]-methyl-(tetrahydro-pyran-4-yl)-amine dihydrochloride (72)

Methyl-[(R)-1-(4-nitro-phenyl)-ethyl]-(tetrahydro-pyran-4-yl)-amine 73 from above (3.2 g, 12 mmol) is stirred with RaNi (1 g) in 100 ml of MeOH. Hydrazine monohydrate (3.2 ml) is added dropwise at room temperature and the reaction mixture is stirred for further 3 hours. After filtration and evaporation under reduced pressure the product is isolated by distribution between Et2O and brine, drying the organic phase with sodium sulfate, filtration and evaporation as yellow oil (2.6 g, 92 %).
MS (ESI): 235 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 7.15 (d, 2H), 6.65 (d, 2H), 4.0 (br m, 2H), 3.7 (br m, 1H), 3.6 (NH_2), 3.3 (br m, 2H), 2.7 (br m, 1H), 2.20 (s, 3H), 1.7 (br m, 4H), 1.30 (d, 3H)

Synthesis of the indole-2-carboxamides

The indole-2-carboxamides are generally prepared by a TBTU-mediated coupling of appropriately substituted indole-2-carboxylic acids with the corresponding amines in the presence of Hünig's base (Reaction Scheme 12).

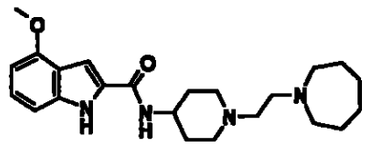
Reaction Scheme 12:



An illustrative example is given below.

Example 1

4-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

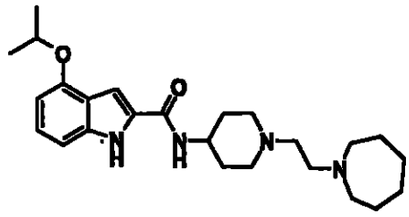


A solution of 4-Methoxy-1H-indole-2-carboxylic acid (930 mg, 4.86 mmol), amine 5 (1.63 g, 4.86 mmol) and DIEA (2.5 ml, 14.58 mmol) in 20 ml of DMF is treated with solid TBTU (1.56 g, 4.86 mmol). The mixture is stirred over night and then evaporated. The crude residue is dissolved in EtOAc and washed twice with sodium bicarbonate (10%). The aqueous layers are re-extracted with DCM, the combined organic layers are washed with brine and dried over sodium sulfate. The crude product is then purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 0% to 2%).
Yield: 0.975 g (50%) of beige powder.
MS (ESI): 399.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.24 (d, 1H), 7.28 (s, 1H), 7.09 (t, 1H), 7.0 (d, 1H), 6.5 (d, 1H), 3.75-3.9 (m, 4H), 2.92-3.25 (m, 8H), 2.73 (m, 2H), 2.27 (m, 2H), 1.52-1.9 (m, 12H).

The formation of the dihydrochlorides can be achieved by treatment of a solution of the free base in DCM or acetone with 2M HCl in ether at 0°C.

Example 2

4-Isopropoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-Isopropoxy-1H-indole-2-carboxylic acid 74 (preparation see below) and amine 5.
MS (ESI): 427.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.24 (d, 1H), 7.22 (d, 1H), 7.06 (t, 1H), 6.98 (d, 1H), 6.51 (d, 1H), 4.75 (m, 1H), 3.75 (m, 1H), 2.99 (m, 2H), 2.53-2.64 (m, 6H), 2.39 (m, 2H), 2.02 (m, 2H), 1.77 (m, 2H), 1.49-1.63 (m, 10H), 1.35 (d, 6H).

Synthesis of 4-Isopropoxy-1H-indole-2-carboxylic acid (74):

(1) Step A: 4-Hydroxy-1H-indole-2-carboxylic acid methyl ester (75)

To an ice cold solution of 4-Methyloxy-1H-indole-2-carboxylic acid methyl ester (1 g, 4.87 mmol) in DCM (10 ml) is added BBr3 (1M in DCM, 4.9 ml, 4.9 mmol). It is stirred for 1 hour and another equivalent (4.9 ml) of BBr3 is added. After another hour, the mixture is poured on ice and the pH is adjusted to 7 with sodium bicarbonate. Extraction with DCM gave a yellow powder.

Yield: 0.82 g (88%). MS (ESI): 192.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.78 (br s, 1H), 9.73 (s, 1H), 7.21 (d, 1H), 7.05 (dd, 1H), 6.89 (d, 1H), 6.4 (d, 1H), 3.86 (s, 3H).

(2) Step B: 4-Isopropoxy-1H-indole-2-carboxylic acid methyl ester (76)

DEAD (0.227 ml, 1.47 mmol) is slowly added to a solution of 4-Hydroxy-1H-indole-2-carboxylic acid methyl ester 75 (200 mg, 1.05 mmol), triphenylphosphine (384 mg, 1.47 mmol) and isopropanol (0.108 ml, 1.43 mmol) in 2 ml of THF. Stirring is continued for 20 minutes and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using cyclohexane/EtOAc (9/1).

Yield: 89 mg (37%). MS (ESI): 234.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.89 (s, 1H), 7.26 (t, 1H), 7.07 (s, 1H), 6.98 (d, 1H), 6.54 (d, 1H), 4.72 (m, 1H), 3.85 (s, 3H), 1.33 (d, 6H).

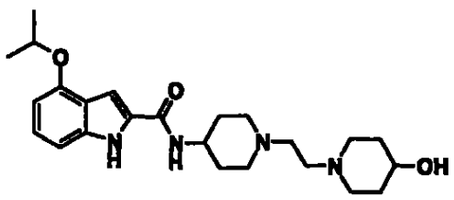
(3) Step C: 4-Isopropoxy-1H-indole-2-carboxylic acid (74)

4-Isopropoxy-1H-indole-2-carboxylic acid methyl ester 76 (114 mg, 0.49 mmol) is dissolved in 5 ml of THF. A 2M-solution of LiOH in water (2.5 ml, 5 mmol) is added and the mixture is stirred for 48 hours. The solvent is then evaporated and the residue is partitioned between water and EtOAc. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a yellow powder.

Yield: 95 mg (89%). MS (ESI): 219.9 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.72 (br s, 1H), 7.14 (dd, 1H), 7.0 (m, 2H), 6.55 (d, 1H), 4.72 (m, 1H), 1.33 (d, 6H).

Example 36b

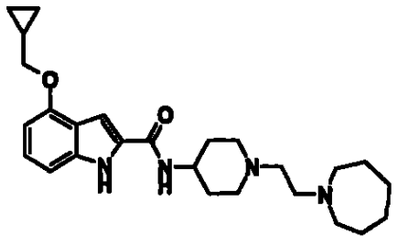
4-Isopropoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-Isopropoxy-1H-indole-2-carboxylic acid 74 (preparation see Example 2) and amine 21.
MS (ESI): 429.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.42 (s, 1H), 8.2 (d, 1H), 7.19 (s, 1H), 7.02 (t, 1H), 6.94 (d, 1H), 6.48 (d, 1H), 4.72 (m, 1H), 4.5 (br. s, 1H), 3.74 (m, 1H), 3.25-3.45 (m, 3H), 2.86 (m, 2H), 2.71 (m, 2H), 2.37 (br. s, 4H), 2.0 (m, 4H), 1.73 (m, 4H), 1.54 (m, 2H), 1.33 (d, 6H).

Example 4

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid 77 (preparation see below) and amine 6.
MS (ESI): 439.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.96 (d, 1H), 6.42 (d, 1H), 3.9 (d, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.76 (m, 2H) 1.47-1.63 (m, 10H), 1.3 (m, 1H), 0.61 (m, 2H), 0.37 (m, 2H).

Synthesis of 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid (77):

(1) Step A: 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid (76)

DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester 79 (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and cyclopropyl-methanol (1.05 ml, 12.26 mmol) in 20 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 95:5). Yield: 1.17 g (46%).

MS (ESI): 260.1 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.85 (s, 1H), 7.4 (s, 1H), 7.19 (t, 1H), 6.99 (d, 1H), 6.45 (d, 1H), 4.4 (q, 2H), 3.95 (d, 2H), 1.41 (t, 3H), 1.34 (m, 1H), 0.66 (m, 2H), 0.4 (m, 2H).

(2) Step B: 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid (77)

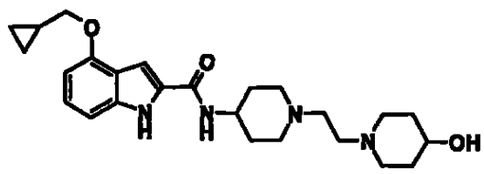
The 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid ethyl ester 78 obtained above is mixed with a 2M-solution of KOH in EtOH (16.9 ml, 33.8 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and DCM. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.

Yield: 1.02 g (99%).

MS (ESI): 232.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.84 (s, 1H), 7.55 (s, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.48 (d, 1H), 3.97 (d, 2H), 1.36 (m, 1H), 0.66 (m, 2H), 0.41 (m, 2H).

Example 5

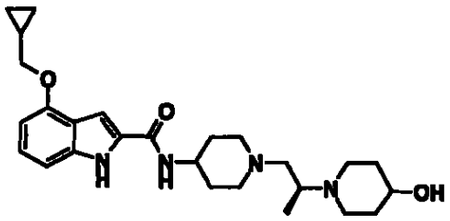
4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid 77 (preparation see Example 4) and amine 21.
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.96 (d, 1H), 6.42 (d, 1H), 4.48 (d, 1H), 3.91 (d, 2H), 3.72 (m, 1H), 3.4 (m, 1H), 2.86 (m, 2H), 2.71 (m, 2H), 2.38 (br. s, 4H) 1.99 (m, 4H), 1.75 (m, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 1.22-1.42 (m, 3H), 0.61 (m, 2H), 0.37 (m, 2H).

Example 6

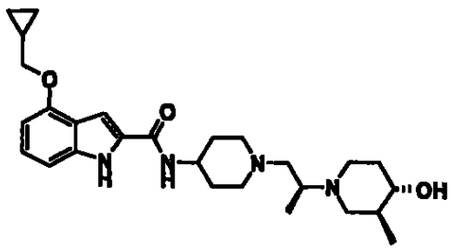
4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclopropylmethoxy-1H-indole-2-carboxylic acid, 77 (see example 4) and amine 50.
MS (ESI): 455.4 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.14 (s, 1H), 6.98 (t, 1H), 6.89 (d, 1H), 6.33 (d, 1H), 3.83 (d, 2H), 3.75 (m, 1H), 3.45 (m, 1H), 2.93 (m, 1H), 2.77 (m, 1H), 2.68 (m, 3H), 2.39 (m, 1H), 2.26 (m, 2H), 2.11 (m, 2H), 1.95 (m, 1H), 1.79 (m, 2H), 1.73 (m, 2H), 1.55 (m, 2H) 1.42 (m, 2H), 1.21 (m, 1H), 0.93 (d, 3H), 0.51 (m, 2H), 0.28 (m, 2H).

Example 7

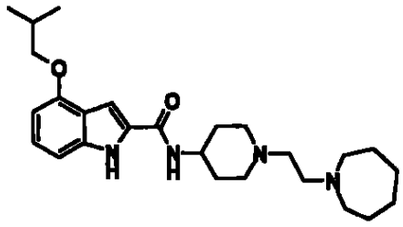
4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclopropylmethoxy-1H-indole-2-carboxylic acid, 77 (see example 4) and amine 56.
MS (ESI): 469.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.95 (d, 1H), 6.41 (d, 1H), 4.44 (d, 1H), 3.91 (d, 2H), 3.74 (m, 1H), 2.61-2.95 (m, 6H), 2.04-2.36 (m, 4H), 1.85-1.97 (m, 2H), 1.66-1.81 (m, 3H), 1.45-1.63 (m, 2H), 1.2-1.43 (m, 3H), 0.91 (d, 3H), 0.87 (d, 3H), 0.61 (m, 2H), 0.37 (m, 2H).

Example 6

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-Isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see below) and amine 5.
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (d, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.46 (d, 1H), 3.84 (d, 2H), 3.75 (m, 1H), 2.99 (m, 1H), 2.53-2.87 (m, 6H), 2.41 (m, 2H), 2.1 (m, 1H), 2.02 (m, 2H) 1.78 (m, 2H), 1.48-1.62 (m, 6H), 1.06 (d, 6H).

Synthesis of 4-Isobutoxy-1H-indole-2-carboxylic acid (80):

(1) **Step A: 4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (79)**

To a solution of 4-Benzyloxy-1H-indole-2-carboxylic acid ethyl ester (29 g, 98.2 mmol) in a mixture of MeOH (750 ml) and DCM (500 ml) is added 1 gram of Pd/C (10%). It is hydrogenated under normal pressure for 24 hours. After filtration and evaporation a white powder is obtained.

Yield: 19.63 g (97%). MS (ESI): 206.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.72 (br s, 1H), 9.69 (s, 1H), 7.2 (s, 1H), 7.05 (t, 1H), 6.98 (d, 1H), 6.38 (d, 1H), 4.33 (q, 2H), 1.32 (t, 3H).

(2) **Step B: 4-Isobutoxy-1H-indole-2-carboxylic acid ethyl ester (81)**

DEAD (10.2 ml, 65.28 mmol) is slowly added to a solution of 4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester 79 (9.57 g, 46.63 mmol), triphenylphosphine (17.12 g, 65.28 mmol) and isobutanol (5.9 ml, 63.42 mmol) in 100 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 3 hours and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using first cyclohexane as eluent, then increasing amounts of EtOAc (from 5% to 50%).

Yield: 8 g (65%).

MS (ESI): 260.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.86 (s, 1H), 7.36 (s, 1H), 7.22 (t, 1H), 6.99 (d, 1H), 6.48 (d, 1H), 4.4 (q, 2H), 3.86 (d, 2H), 2.2 (m, 1H), 1.42 (t, 3H), 1.09 (d, 6H).

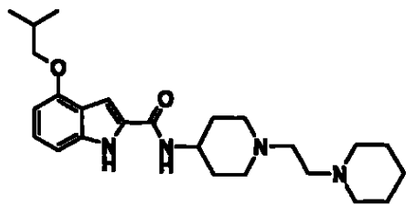
(3) **Step C: 4-Isobutoxy-1H-indole-2-carboxylic acid (80)**

4-Isobutoxy-1H-indole-2-carboxylic acid ethyl ester 81 (5.2 g, 19.9 mmol) is mixed with a 1M-solution of KOH in EtOH (99.5 ml, 99.5 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a beige powder.

Yield: 4.32 g (93%). MS (ESI): 234.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.74 (br s, 1H), 7.13 (dd, 1H), 7.06 (s, 1H), 7.0 (d, 1H), 6.49 (d, 1H), 3.85 (d, 2H), 3.35 (br s, 1H), 2.1 (m, 1H), 1.03 (d, 6H).

Example 9

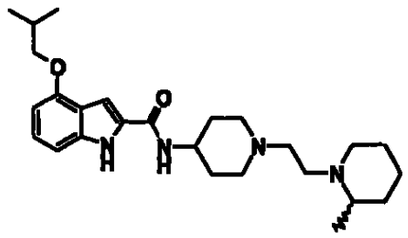
4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 1.
MS (ESI): 427.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (d, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 3.84 (d, 2H), 3.75 (m, 1H), 2.88 (m, 2H), 2.38 (m, 8H), 2.1 (m, 1H), 2.02 (m, 2H), 1.78 (m, 2H), 1.32-1.63 (m, 9H), 1.07 (d, 6H).

Example 10

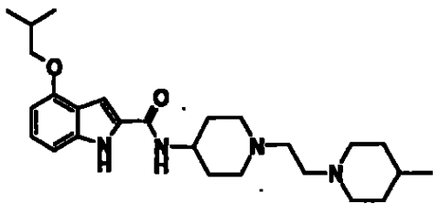
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(RS)-2-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 10.
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (d, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 3.85 (d, 2H), 3.75 (m, 1H), 2.65-2.93 (m, 7H), 2.05-2.43 (m, 5H), 2.01 (m, 2H), 1.78 (m, 2H), 1.1-1.62 (m, 6H), 1.06 (d, 6H), 1.01 (d, 3H).

Example 11

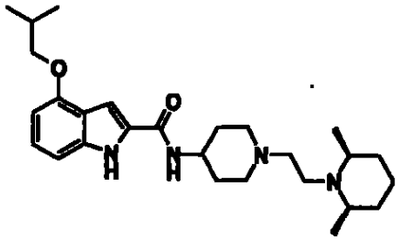
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 7.
MS (ESI): 441.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.2 (d, 1H), 7.22 (d, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 3.86 (d, 2H), 3.75 (m, 1H), 2.86 (m, 4H), 2.4 (br s, 4H), 2.11 (m, 1H), 2.02 (m, 2H), 1.9 (m, 2H), 1.79 (m, 2H), 1.55 (m, 4H), 1.3 (m, 1H), 1.11 (m, 2H), 1.06 (d, 6H), 0.88 (d, 3H).

Example 12

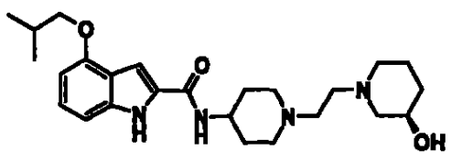
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(2,6-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 27.
MS (ESI): 455.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.2 (d, 1H), 7.22 (d, 1H), 7.04 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 3.85 (d, 2H), 3.75 (m, 1H), 2.87 (m, 2H), 2.7 (m, 2H), 2.43 (m, 2H), 2.32 (m, 2H), 2.1 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.45-1.85 (m, 5H), 1.0-1.35 (m, 16H).

Example 13

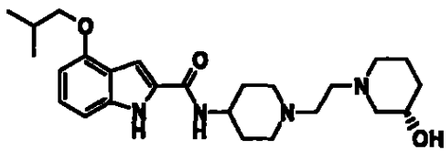
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((R)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 12.
MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (s, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.54 (d, 1H), 3.84 (d, 1H), 3.75 (m, 1H), 3.42 (m, 1H), 2.82-2.93 (m, 2H), 2.49 (br s, 4H), 2.1 (m, 1H), 2.0 (m, 2H), 1.3-1.9 (m, 11H), 1.06 (d, 6H).

Example 14

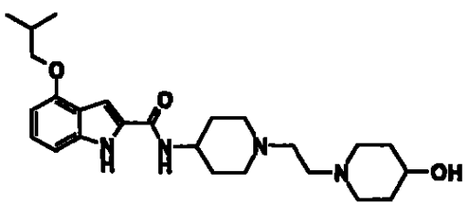
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((S)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is obtained by preparative separation of racemic material using a chiral HPLC stationary phase (CHIRALCEL OJ-H 1170). The absolute stereochemistry is assigned by comparison with the enantiomerically defined (R)-isomer of example 13.

Example 15

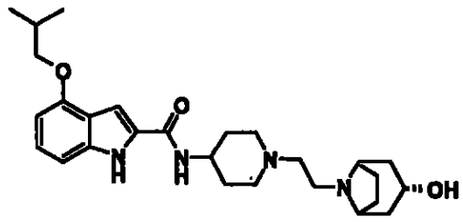
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 21.
MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Example 16

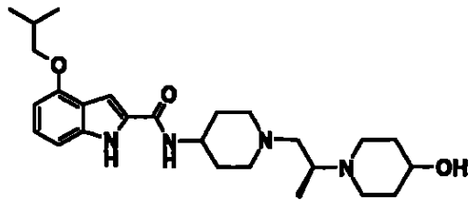
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 24.
MS (ESI): 469.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.23 (d, 1H), 7.72 (s, 1H), 6.9-7.1 (m, 2H), 6.46 (d, 1H), 4.57 (br s, 1H), 3.85 (d, 2H), 3.77 (m, 1H), 3.2-3.7 (br m, 4H), 2.94 (m, 2H), 2.75 (m, 2H), 2.56 (m, 2H), 1.5-2.25 (m, 15H), 1.06 (d, 6H).

Example 17

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

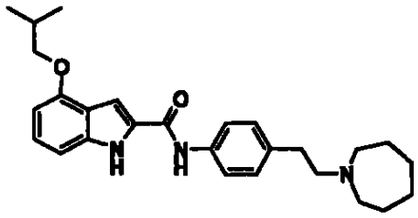


This compound is synthesized analogously to example 1 from 4-isobutoxy-1H-indole-2-carboxylic acid, 80 (see example 8) and amine 50.

MS (ESI): 457.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (d, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.44 (d, 1H), 4.47 (d, 1H), 3.84 (d, 2H), 3.73 (m, 1H), 3.37 (m, 1H), 2.6-2.95 (m, 5H), 2.05-2.38 (m, 6H), 1.92 (m, 1H), 1.76 (m, 2H), 1.69 (m, 2H), 1.2-1.65 (m, 4H), 1.05 (d, 6H), 0.92 (d, 3H).

Example 18

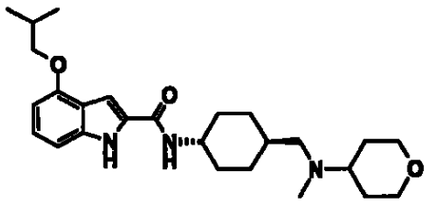
4-Isobutoxy-1H-indole-2-carboxylic acid [4-(2-azepan-1-yl-ethyl)-phenyl]-amide



This compound is synthesized analogously to Example 1 from 4-Isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 70.
MS (ESI): 434.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 10.07 (s, 1H), 7.67 (d, 2H), 7.48 (d, 1H), 7.18 (d, 2H), 7.08 (t, 1H), 7.01 (d, 1H), 6.49 (d, 1H), 3.88 (d, 2H), 2.57-2.62 (m, 8H), 2.13 (m, 2H), 1.48-1.63 (m, 8H), 1.08 (d, 6H).

Example 19

4-Isobutoxy-1H-indole-2-carboxylic acid (4-[[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl]-cyclohexyl)-amide

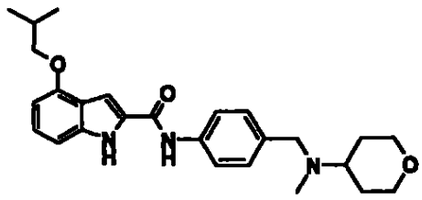


This compound is synthesized analogously to Example 1 from 4-Isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and trans-4-Amino-cyclohexylmethyl)-methyl-(tetrahydro-pyran-4-yl)-amine (WO2000068203)

MS (ESI): 442.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.18 (d, 1H), 7.23 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 3.82-3.93 (m, 4H), 3.74 (m, 1H), 3.22-3.31 (m, 2H), 2.7 (s, 3H), 2.45 (m, 1H), 2.18 (m, 4H), 2.11 (m, 1H), 1.85 (m, 4H), 1.6 (m, 2H), 1.2-1.48 (m, 5H), 1.06 (d, 6H).

Example 20

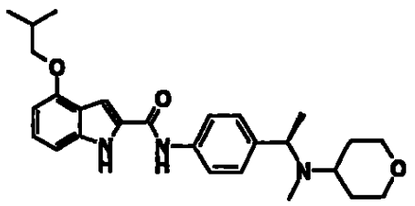
4-Isobutoxy-1H-indole-2-carboxylic acid (4-[[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl]-phenyl)-amide



This compound is synthesized analogously to Example 1 from 4-Isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and (4-Amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine (WO9932468).
MS (ESI): 436.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 10.12 (s, 1H), 7.74 (d, 2H), 7.5 (s, 1H), 7.27 (d, 2H), 7.09 (t, 1H), 7.02 (d 1H), 6.5 (d, 1H), 3.84-3.94 (m, 4H), 3.52 (s, 2H), 3.22-3.32 (m, 2H), 2.6 (m, 1H), 2.08-2.2 (m, 4H), 1.72 (m, 2H), 1.53 (m, 2H), 1.07 (d, 6H).

Example 21

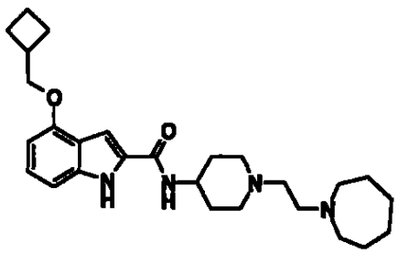
4-Isobutoxy-1H-indole-2-carboxylic acid (4-[(R)-1-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl]-phenyl)-amide



This compound is synthesized analogously to Example 1 from 4-Isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8) and amine 72.
MS (ESI): 450.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.66 (s, 1H), 10.12 (s, 1H), 7.73 (d, 2H), 7.5 (d, 1H), 7.3 (d, 2H), 7.09 (t, 1H), 7.02 (d, 1H), 6.5 (d, 1H), 3.76-3.91 (m, 5H), 3.1-3.33 (m, 2H), 2.66 (m, 1H), 2.04-2.2 (m, 4H), 1.36-1.68 (m, 4H), 1.28 (d, 3H), 1.08 (d, 6H).

Example 22

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid 82 (preparation see below) and amine 5.
MS (ESI): 453.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.05 (d, 2H), 3.74 (m, 1H), 2.86 (m, 2H), 2.78 (m, 1H), 2.55-2.7 (m, 6H), 2.4 (m, 2H), 1.83-2.18 (m, 8H), 1.76 (m, 2H) 1.47-1.63 (m, 10H).

Synthesis of 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid (82):

(1) **Step A: 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid (83)**

DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester 79 (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and cyclobutyl-methanol (1.25 ml, 12.26 mmol) in 20 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 95:5).

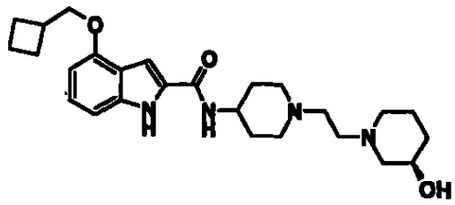
Yield: 1.86 g (70%). MS (ESI): 274.2 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.83 (s, 1H), 7.35 (s, 1H), 7.21 (t, 1H), 6.98 (d, 1H), 6.49 (d, 1H), 4.4 (q, 2H), 4.07 (d, 2H), 2.85 (m, 1H), 2.17 (m, 2H), 1.95 (m, 4H), 1.42 (t, 3H).

(2) Step B: 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid (82)

The 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid ethyl ester 83 obtained above is mixed with a 2M-solution of KOH in EtOH (16.9 ml, 33.8 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and DCM. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.
Yield: 1.65 g (99%). MS (ESI): 246.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 11.74 (br. s, 1H), 7.14 (t, 1H), 7.03 (s, 1H), 6.99 (d, 1H), 6.51 (d, 1H), 4.05 (d, 2H), 2.8 (m, 1H), 2.11 (m, 2H), 1.93 (m, 4H).

Example 23

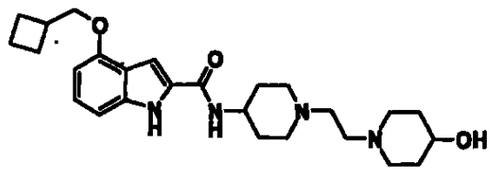
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid 82 (preparation see Example 22) and amine 12.
MS (ESI): 455.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.22 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.47 (d, 1H), 4.56 (br s, 1H), 4.05 (d, 2H), 3.75 (m, 1H), 3.43 (m, 1H), 2.88 (m, 3H), 2.78 (m, 1H), 2.68 (m, 1H), 2.42 (br. s, 4H), 1.83-2.2 (m, 8H), 1.77 (m, 4H), 1.56 (m, 4H), 1.38 (m, 2H).

Example 24

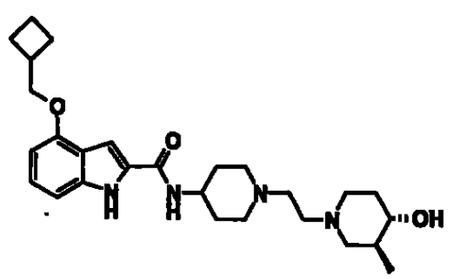
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid 82 (preparation see Example 22) and amine 21.
MS (ESI): 455.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.49 (s, 1H), 4.05 (d, 2H), 3.73 (m, 1H), 3.41 (m, 1H), 2.87 (m, 2H), 2.78 (m, 1H), 2.7 (m, 2H), 2.38 (m, 4H) 2.14 (m, 2H), 1.83-2.07 (m, 8H), 1.76 (m, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 1.35 (m, 2H).

Example 25

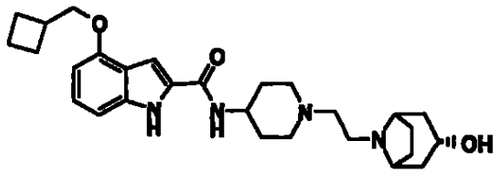
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid, 82 (see example 22) and amine 14.
MS (ESI): 469.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 4.48 (d, 1H), 4.04 (d, 2H), 3.73 (br m, 1H), 2.64-2.97 (m, 6H), 2.37 (m, 4H), 2.05-2.2 (m, 2H), 1.81-2.05 (m, 7H), 1.65-1.81 (m, 3H), 1.46-1.65 (m, 3H), 1.27-1.46 (m, 2H), 0.88 (d, 3H).

Example 26

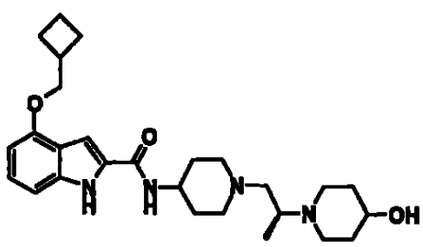
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid 82 (preparation see Example 22) and amine 24.
MS (ESI): 481.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.31 (br s, 1H), 4.04 (d, 2H), 3.8 (br. S, 1H), 3.74 (m, 1H), 2.89 (m, 2H), 2.78 (m, 1H), 2.42 (br. m, 6H), 1.7-2.2 (m, 16H), 1.56 (m, 4H).

Example 27

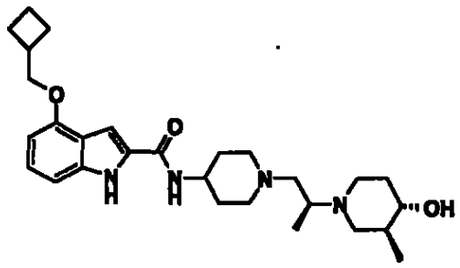
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid, 82 (see example 22) and amine 50.
MS (ESI): 469.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.18 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 4.46 (d, 1H), 4.05 (d, 2H), 3.74 (m, 1H), 3.36 (m, 1H), 2.6-2.95 (m, 6H), 2.04-2.4 (m, 7H), 1.83-2.0 (m, 4H), 1.64-1.81 (m, 4H), 1.45-1.63 (m, 2H), 1.23-1.42 (m, 2H), 0.92 (d, 3H).

Example 28

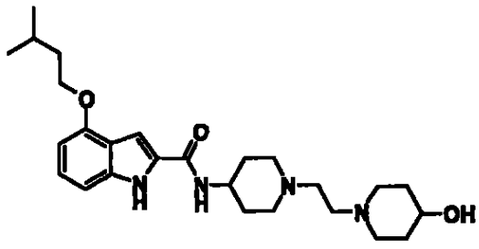
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid, 82 (see example 22) and amine 56.
MS (ESI): 483.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.22 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 4.44 (d, 1H), 4.04 (d, 2H), 3.74 (m, 1H), 2.6-2.95 (m, 7H), 2.33 (m, 1H), 2.24 (m, 1H), 2.02-2.19 (m, 4H), 1.82-2.01 (m, 6H), 1.66-1.81 (m, 3H), 1.45-1.64 (m, 2H), 1.2-1.43 (m, 2H), 0.91 (d, 3H), 0.87 (d, 3H).

Example 29

4-(3-Methyl-butyloxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride



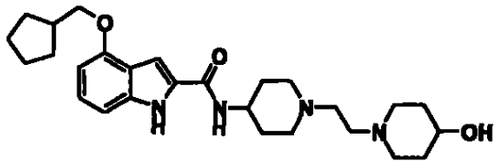
This compound is synthesized analogously to Example 1 from 4-(3-methyl-butyloxy)-1H-indole-2-carboxylic acid (84) (preparation see below) and amine 21.
Yield: 110 mg (43%). MS (ESI): 457 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.4 (s, 1H), 10.5 – 10.8 (br, 2H), 8.58 (d, 1H), 7.22 (s, 1H), 7.05 (dd, 1H), 6.95 (d, 1H), 6.48 (d, 1H), 4.1 (t, 2H), 3.4 – 3.75 (m, 9H), 2.9 – 3.2 (m, 4H), 1.65 – 2.1 (m, 11H), 0.95 (d, 6H).

Synthesis of 4-(3-methyl-butyloxy)-1H-indole-2-carboxylic acid (84):

This compound is synthesized analogously to (85) from 3-methyl-butan-1-ol.
Yield: 0.54 g (100%). MS (ESI): 246 [M-H]⁻.

Example 30

4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid 86 (preparation see below) and amine 21.
MS (ESI): 469.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.42 (s, 1H), 8.19 (d, 1H), 7.18 (s, 1H), 7.01 (t, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 4.48 (br. s, 1H), 3.93 (d, 2H), 3.72 (m, 1H), 3.4 (m, 1H), 3.15 (br.s, 1H), 2.86 (m, 2H), 2.7 (m, 2H), 2.37 (m, 4H) 1.99 (m, 4H), 1.25-1.88 (m, 16H).

Synthesis of 4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid (86):

(1) **Step A: 4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid ethyl ester (87)**

DEAD (5.3 ml, 34.1 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester 79 (2 g, 24.36 mmol), triphenylphosphine (8.95 g, 34.1 mmol) and cyclopentyl-methanol (3.58 ml, 33.13 mmol) in 30 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 90:10).

Yield: 3.88 g (55%). MS (ESI): 288.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.86 (br. s, 1H), 7.35 (s, 1H), 7.21 (t, 1H), 6.98 (d, 1H), 6.48 (d, 1H), 4.4 (q, 2H), 3.98 (d, 2H), 2.47 (m, 1H), 1.89 (m, 2H), 1.85 (m, 4H), 1.42 (t, 3H and overlapping m, 2H).

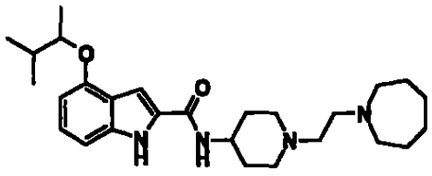
(2) Step B: 4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid (86)

The 4-cyclopentylmethoxy-1H-indole-2-carboxylic acid ethyl ester 87 obtained above is mixed with a 2M-solution of KOH in EtOH (33.8 ml, 67.6 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.

Yield: 2.55 g (73%). MS (ESI): 260.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.73 (br. s, 1H), 7.12 (t, 1H), 7.02 (s, 1H), 6.96 (d, 1H), 6.5 (d, 1H), 3.96 (d, 2H), 2.39 (m, 1H), 1.82 (m, 2H), 1.6 (m, 4H), 1.4 (m, 2H).

Example 31

4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid 88 (preparation see below) and amine 5.

MS (ESI): 455.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.4 (s, 1H), 8.2 (d, 1H), 7.18 (d, 1H), 7.02 (dd, 1H), 6.93 (d, 1H), 6.47 (d, 1H), 4.37 (m, 1H), 3.74 (m, 1H), 2.88 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 1.89-2.06 (m, 3H), 1.75 (m, 2H), 1.46-1.62 (m, 10H), 1.24 (d, 3H), 1.0 (m, 6H).

Synthesis of 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid (88):

(1) Step A: 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid ethyl ester (89)

DEAD (5.3 ml, 34.1 mmol) is slowly added to a solution of 4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester 79 (5 g, 24.36 mmol), triphenylphosphine (8.95 g, 34.1 mmol) and 3-Methyl-butan-2-ol (3.58 ml, 33.13 mmol) in 50 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 3 days and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using first cyclohexane as eluent, then increasing amounts of EtOAc (from 5% to 50%).

Yield: 2.4 g (36%). MS (ESI): 276.3 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.9 (br s, 1H), 7.35 (s, 1H), 7.2 (dd, 1H), 6.96 (d, 1H), 6.5 (d, 1H), 4.4 (q, 2H), 4.34 (t, 1H), 2.03 (m, 1H), 1.42 (t, 3H), 1.31 (d, 3H), 1.04 (m, 6H).

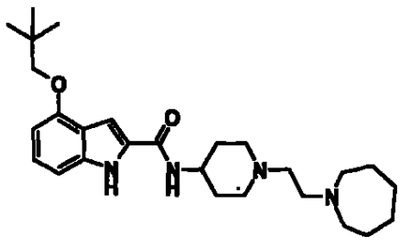
(2) Step B: 4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid (88)

4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid ethyl ester 89 (2.4 g, 8.72 mmol) is mixed with a 1M-solution of KOH in EtOH (43.6 ml, 87.2 mmol) and stirred for 48 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a beige powder.

Yield: 2.14 g (99%). MS (ESI): 248.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.92 (br s, 1H), 7.52 (s, 1H), 7.27 (m, 1H), 6.99 (d, 1H), 6.51 (d, 1H), 4.34 (m, 1H), 2.02 (m, 1H), 1.33 (d, 3H), 1.04 (m, 6H).

Example 32

4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid 85 (preparation see below) and amine 5.
MS (ESI): 455.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.25 (d, 1H), 7.25 (d, 1H), 7.06 (t, 1H), 6.99 (d, 1H), 6.48 (d, 1H), 3.72-3.84 (m, 3H), 2.92 (m, 1H), 2.54-2.63 (m, 6H), 2.41 (m, 2H), 2.04 (m, 2H), 1.79 (m, 2H), 1.5-1.65 (m, 11H), 1.1 (s, 9H).

Synthesis of 4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid (85):

(1) Step A: 4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid methyl ester (90)

DEAD (0.414 ml, 2.66 mmol) is slowly added to a solution of 4-Hydroxy-1H-indole-2-carboxylic acid methyl ester 75 (363 mg, 1.9 mmol), triphenylphosphine (698 mg, 2.66 mmol) and 2,2-Dimethyl-propan-1-ol (228 mg, 2.58 mmol) in 8 ml of THF. Stirring is continued for 20 hours and the solvent is then evaporated. The crude mixture is purified by chromatography on silicagel using cyclohexane/EtOAc (9/1).
Yield: 271 mg (55%). MS (ESI): 261.9 $[M+H]^+$, 1H-NMR ($CDCl_3$): δ (ppm) 8.9 (br s, 1H), 7.39 (s, 1H), 7.23 (dd, 1H), 7.0 (d, 1H), 6.47 (d, 1H), 3.95 (s, 3H), 3.74 (s, 2H), 1.0 (s, 9H).

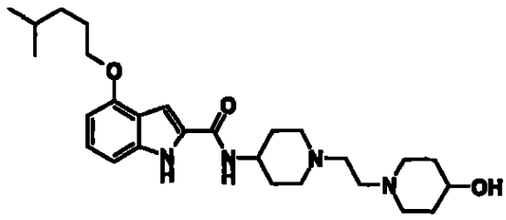
(2) Step B: 4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid (85)

4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid methyl ester 90 (270 mg, 1.03 mmol) is dissolved in 20 ml of THF. A 2M-solution of LiOH in water (5.2 ml, 11 mmol) is added and the mixture is stirred for 48 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a yellow powder.

Yield: 230 mg (90%). MS (ESI): 248.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (br s, 1H), 7.13 (dd, 1H), 7.08 (s, 1H), 7.0 (d, 1H), 6.49 (d, 1H), 4.74 (s, 2H), 1.07 (s, 9H).

Example 33

4-(4-Methyl-pentyloxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride



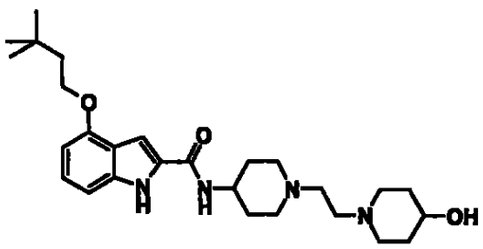
This compound is synthesized analogously to Example 1 from 4-(4-methyl-pentyloxy)-1H-indole-2-carboxylic acid (91) (preparation see below) and amine 21.
Yield: 145 mg (70%). MS (ESI): 471 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4 – 10.7 (br, 2H), 8.58 (d, 1H), 7.25 (s, 1H), 7.05 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 3.95 – 4.2 (m, 4H), 2.95 – 3.8 (m, 12H), 1.7 – 2.1 (m, 10H), 1.6 (m, 2H), 1.35 (m, 2H), 0.9 (d, 6H).

Synthesis of 4-(4-methyl-pentyloxy)-1H-indole-2-carboxylic acid (91):

This compound is synthesized analogously to (86) from 4-methyl-pentan-1-ol.
Yield: 0.61 g (94%). MS (ESI): 260 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.8 (s, 1H), 11.65 (s, 1H), 7.1 (dd, 1H), 7.0 (s, 1H), 6.98 (d, 1H), 6.48 (d, 1H), 4.05 (t, 2H), 1.77 (t, 2H), 1.63 (m, 1H), 1.35 (m, 2H), 0.9 (d, 6H).

Example 34

4-(3,3-Dimethyl-butoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride



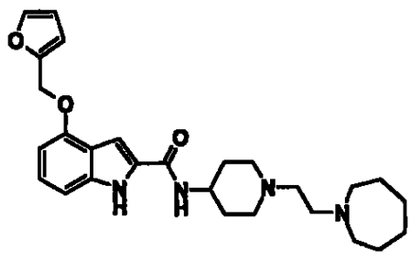
This compound is synthesized analogously to Example 1 from 4-(3,3-dimethyl-butoxy)-1H-indole-2-carboxylic acid (92) (preparation see below) and amine 21.
Yield: 60 mg (24%). MS (ESI): 471 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.4 (s, 1H), 10.5 (br, 1H), 8.58 (d, 1H), 7.17 (s, 1H), 7.0 – 7.1 (m, 2H), 6.5 (d, 1H), 4.2 (m, 2H), 4.15 (m, 1H), 3.85 (m, 1H), 3.65 (m, 4H), 3.1 – 3.5 (m, 8H), 2.0 – 2.2 (m, 6H), 1.75 – 1.85 (m, 4H), 1.03 (s, 9H).

Synthesis of 4-(3,3-Dimethyl-butoxy)-1H-indole-2-carboxylic acid (92):

This compound is synthesized analogously to (85) from 3,3-dimethyl-butan-1-ol.
Yield: 1.1 g (100%). MS (ESI): 260 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.8 (s, 1H), 11.65 (s, 1H), 7.12 (dd, 1H), 6.98 (s, 1H), 6.95 (d, 1H), 6.52 (d, 1H), 4.13 (t, 2H), 1.75 (t, 2H), 1.0 (s, 9H).

Example 35

4-(Furan-2-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid 93 (preparation see below) and amine 5.
MS (ESI): 466.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.13 (d, 1H), 7.71 (s, 1H), 7.23 (s, 1H), 7.06 (t, 1H), 7.0 (d, 1H), 6.63 (m, 2H), 6.48 (s, 1H), 5.13 (s, 2H), 3.72 (m, 1H), 2.86 (m, 2H), 2.5-2.6 (m, 6H), 2.36 (m, 2H), 2.0 (m, 2H), 1.74 (m, 2H) 1.45-1.6 (m, 10H).

Synthesis of 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid (93):

(1) **Step A: 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester (94)**

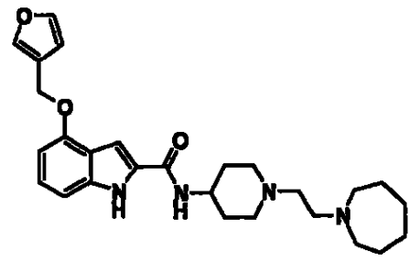
DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester 79 (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and furan-2-yl-methanol (1.18 ml, 12.26 mmol) in 10 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is purified by chromatography (cyclohexane:EtOAc / 95:5).
Yield: 0.76 g (27%).

(2) **Step B: 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid (93)**

The 4-(furan-2-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester 94 obtained above is mixed with a 1M-solution of KOH in EtOH (13.3 ml, 13.3 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.
Yield: 0.329 mg (48%). 1H-NMR (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.73 (s, 1H), 7.69 (s, 1H), 7.14 (t, 1H), 7.02 (d, 1H), 6.98 (s, 1H), 6.68 (d, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 5.16 (s, 2H).

Example 36

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid 95 (preparation see below) and amine 5.
MS (ESI): 465.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.06 (t, 1H), 6.99 (d, 1H), 6.82 (s, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H) 1.45-1.62 (m, 10H).

Synthesis of 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid (95):

(1) Step A: 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester (96)

DEAD (2.1 ml, 13.65 mmol) is slowly added to a solution of 4-hydroxy-1H-indole-2-carboxylic acid ethyl ester 79 (2 g, 9.75 mmol), triphenylphosphine (3.58 g, 13.65 mmol) and furan-3-yl-methanol (1.18 ml, 12.26 mmol) in 10 ml of THF, so that the temperature always remained below 30 0C. Stirring is continued for 2 hours and the solvent is then evaporated. The crude residue is triturated with ether and the white precipitate is filtered off. It contained mainly product. The mother liquor is purified by chromatography (cyclohexane:EtOAc / 95:5) and combined with the first precipitate. Yield: 3 g (>100%).

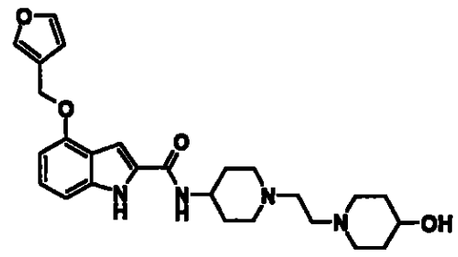
(2) Step B: 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid (95)

The 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid ethyl ester 96 obtained above is mixed with a 1M-solution of KOH in EtOH (35 ml, 35 mmol) and stirred for 24 hours. The solvent is then evaporated and the residue is partitioned between water and ether. The water layer is acidified with HCl and extracted twice with EtOAc. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to give a white powder.

Yield: 1.63 g (65%). MS (ESI): 258.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.71 (s, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 7.13 (m, 1H), 7.01 (m, 2H), 6.62 (m, 2H), 5.07 (s, 2H).

Example 37

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

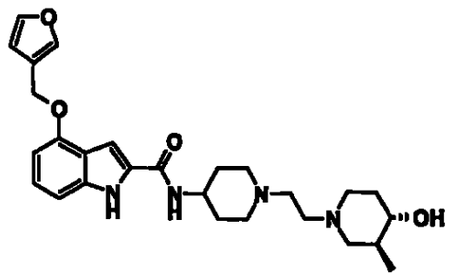


This compound is synthesized analogously to example 1 from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid 95 (see example 36) and amine 21.

MS (ESI): 467 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.13 (d, 1H), 7.81 (s, 1H), 7.68 (t, 1H), 7.22 (d, 1H), 7.08 (t, 1H), 6.98 (d, 1H), 6.62 (s, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 4.48 (d, 1H), 3.73 (m, 1H), 3.4 (m, 1H), 2.86 (m, 2H), 2.7 (m, 2H), 2.38 (br. s, 4H) 2.0 (m, 4H), 1.72 (m, 4H), 1.52 (m, 2H), 1.35 (m, 2H).

Example 38

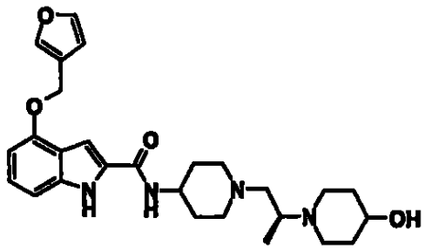
4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid 95 (preparation see example 36) and amine 14.
MS (ESI): 481.2 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.63 (s, 1H), 7.51 (s, 1H), 7.23 (s, 1H), 7.13 (t, 1H), 7.04 (d, 1H), 6.6 (d, 1H), 6.57 (s, 1H), 5.08 (s, 2H), 3.9 (m, 1H), 2.83-3.12 (m, 5H), 2.55 (m, 4H), 2.21 (m, 2H), 2.11 (m, 1H), 1.84-2.0 (m, 3H), 1.51-1.83 (m, 5H), 0.99 (d, 3H).

Example 39

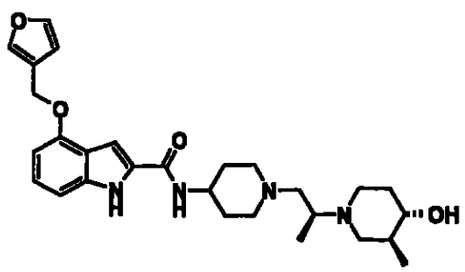
4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid, 95 (see example 36) and amine 50.
MS (ESI): 481.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.60 (d, 1H), 5.03 (d, 2H), 4.45 (d, 1H), 3.73 (m, 1H), 3.37 (m, 1H), 2.9 (m, 1H), 2.8 (m, 1H), 2.6-2.75 (m, 3H), 2.05-2.37 (m, 5H), 1.9 (m, 1H), 1.65-1.8 (m, 4H), 1.42-1.62 (m, 2H), 1.2-1.4 (m, 2H), 0.92 (d, 3H).

Example 40

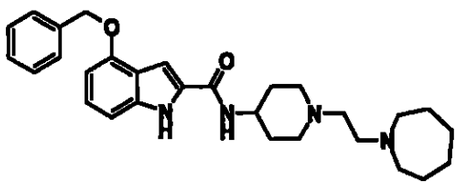
4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid, 95 (see example 36) and amine 56.
MS (ESI): 495.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.23 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 4.43 (d, 1H), 3.72 (m, 1H), 2.58-2.94 (m, 5H), 2.32 (m, 1H), 2.24 (m, 1H), 2.03-2.19 (m, 2H), 1.84-1.96 (m, 2H), 1.66-1.79 (m, 3H), 1.42-1.62 (m, 2H), 1.2-1.41 (m, 3H), 0.91 (d, 3H), 0.86 (d, 3H).

Example 41

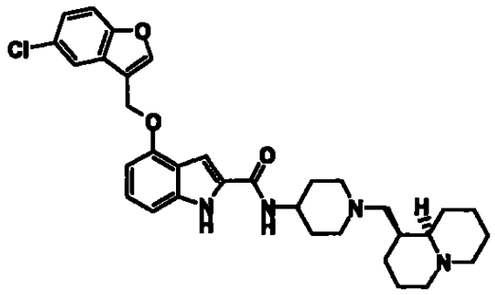
4-Benzyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-Benzyloxy-1H-indole-2-carboxylic acid and amine 5.
MS (ESI): 475.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.16 (d, 1H), 7.3-7.54 (m, 5H), 7.26 (d, 1H), 7.06 (t, 1H), 7.0 (d, 1H), 6.6 (d, 1H), 5.18 (s, 2H), 3.74 (m, 1H), 2.86 (m, 2H), 2.47-2.62 (m, 8H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.45-1.64 (m, 10H).

Example 42

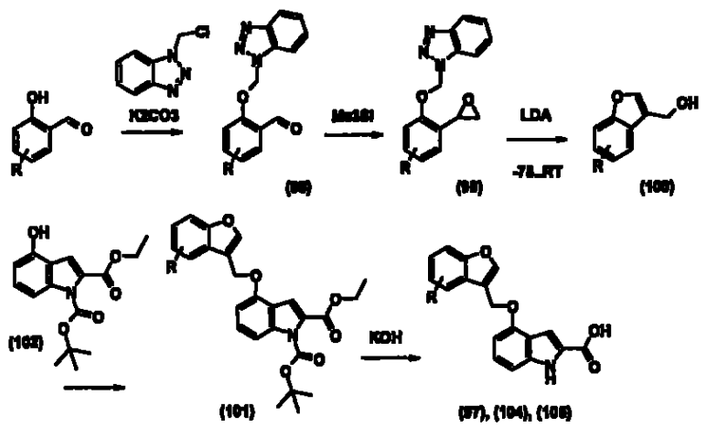
4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97) (preparation see below) and amine 61 analogously to the method described in example 1.

Yield: 200 mg (59%). MS (ESI): 575 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.1 – 10.7 (m, 2H), 8.5 (t, 1H), 8.24 (s, 1H), 7.75 (d, 1H), 7.68 (d, 1H), 7.37 (dd, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.8 – 3.6 (m, 14H), 1.3 – 2.1 (m, 12H).

Reaction Scheme 13:



Synthesis of 4-Hydroxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (102):

(1) **Step A: 4-Benzyloxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (103)**

4-Benzyloxy-1H-indole-2-carboxylic acid ethyl ester (50 g, 169.3 mmol) is dissolved in 500 ml of ethyl acetate and DMAP (141 mg, 3.4 mmol) is added. Then the mixture is cooled to 0°C and BOC_2O (36.9 g, 169.3 mmol), dissolved in 20 ml of ethyl acetate, is added dropwise. After completion of addition the reaction mixture is allowed to stir over night at room temperature. The mixture is washed with 1M tartaric acid and brine. The organic layers are dried over sodium sulfate and evaporated

Yield: 72 g of a colorless oil, which is used in the next step without further purification.
MS (ESI): 396 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.51 (m, 1H), 7.47 (m, 2H), 7.40 (m, 1H), 7.38 (m, 2H), 7.31 (m, 1H), 7.21 (s, 1H), 6.92 (d, 1H), 5.28 (s, 2H), 4.28 (q, 2H), 1.56 (s, 9H), 1.31 (t, 3H).

(2) **Step B: 4-Hydroxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (102)**

103 (46.2 g, 116.6 mmol) is dissolved in ethanol (300 ml) and after addition of ammonium formiate (8.3 g, 128.5 mmol) and 10% Pd-C (5 g) the mixture is stirred at room temperature for 1 h. Then the mixture is filtered off. Evaporation under reduced pressure gave 6.89 g of a white solid, which is further purified by recrystallisation from ether / hexanes.
Yield: 27.75 g (78%). MS (ESI): 304 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 10.1 (s, 1H), 7.38 (d, 1H), 7.25 (s, 1H), 7.23 (dd, 1H), 6.65 (d, 1H), 4.3 (q, 2H), 1.55 (s, 9H), 1.3 (t, 3H).

Synthesis of 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97):

(1) **Step A: 2-(Benzotriazol-1-ylmethoxy)-5-chloro-benzaldehyde (98)**

5-Chloro-2-hydroxy-benzaldehyde (8.45 g, 54 mmol) is dissolved in DMF (100 ml) and after addition of 1-(chlormethyl)-1H-benzotriazole (9.96 g, 59.4 mmol) and K_2CO_3 (9.7 g, 70.2 mmol) the mixture is stirred at 45°C for 1 h (TLC control). Then the mixture is evaporated under high vacuum. The residue is diluted with ethyl acetate, washed with brine and dried

over Na_2SO_4. Evaporation gave 3.9 g of a colorless solid. The product is used in the next step without further purification.
Yield: 17 g (100%) of a white solid. MS (ESI): 288 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 10.01 (s, 1H), 8.08 (d, 1H), 7.97 (d, 1H), 7.78 (dd, 1H), 7.68 (d, 1H), 7.62 (dd, 1H), 7.55 (d, 1H), 7.43 (dd, 1H), 6.95 (s, 2H).

(2) Step B: 1-(4-Chloro-2-oxiranyl-phenoxymethyl)-1H-benzotriazole (99)

98 (15.5 g, 54 mmol) is dissolved in 150 ml of DCM and 150 ml of 40% aqueous sodium hydroxide solution. After addition of trimethylsulfonium iodide (14.3 g, 70.2 mmol) and tetrabutylammoniumiodide (1.4 g, 3.8 mmol), the mixture is refluxed for 18h. The reaction mixture is diluted with DCM, washed with water and the organic layers are dried over Na_2SO_4. Evaporation gave 18.7 g of a yellow oil, which is further purified by flash-chromatography (silicagel, ethyl acetate / hexanes 3:7)
Yield: 11.7 g (72%) of a colorless oil. MS (ESI): 302 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.08 (d, 1H), 7.92 (d, 1H), 7.62 (dd, 1H), 7.5 (dd, 1H), 7.45 (dd, 1H), 7.4 (dd, 1H), 6.92 (d, 1H), 6.83 (dd, 1H), 3.8 (m, 1H), 2.8 (dd, 2H), 2.48 (dd, 1H).

(3) Step C: (5-Chloro-benzofuran-3-yl)-methanol (100)

99 (25.7 g, 85.1 mmol) is dissolved in 300 ml of tetrahydrofurane and cooled to -78°C. A 2M solution of LDA in THF (93.7 ml, 187.4 mmol) is added dropwise within 45 min. The reaction mixture is allow to warmup to room temperature within 17 h. Then the reaction mixture is quenched with saturated aqueous ammonium chloride solution and evaporated under reduced pressure. The residue is diluted with ethyl acetate, washed with water and brine and dried over sodium sulfate. Evaporation gave 17.2 g of an brown resin which is further purified by flash-chromatography (silicagel, ethyl acetate / hexanes 2:8).
Yield: 10.4g mg of a white solid (67%). MS (ESI): 181 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 7.91 (d, 1H), 7.72 (d, 1H), 7.56 (d, 1H), 7.32 (dd, 1H), 5.18 (t, 1H), 4.58 (d, 2H).

(4) Step D: 4-(5-Chloro-benzofuran-3-ylmethoxy)-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (101)

100 (4 g, 21.9 mmol), 102 (6.7 g, 21.9 mmol), triphenylphosphine (17.3 g, 65.8 mmol) and 40% diethyl azadicarboxylate solution (31.8 ml, 65.8 mmol) are dissolved in THF and cooled

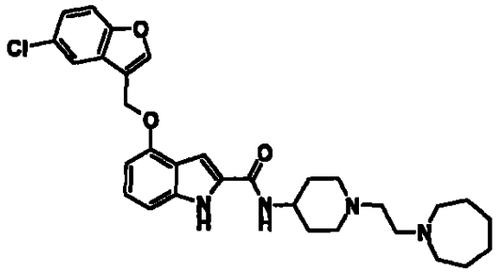
to 0°C. Then a solution of N-ethyldiisopropylamine (11.2 ml, 65.8 mmol) in THF is added dropwise. After the addition is completed, the mixture is stirred at room temperature for 2 h. Then the mixture is evaporated under reduced pressure. The residue is diluted with ethyl acetate, washed with saturated NaHCO3-solution and dried over Na2SO4. The crude product is purified by Flash-chromatography (ethyl acetate / hexanes (3:7), silicagel).
Yield: 7.7 g (75%) of a slightly colored oil. MS (ESI): 469 $[M]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.27 (s, 1H), 7.79 (d, 1H), 7.63 (d, 1H), 7.53 (d, 1H), 7.40 (d, 1H), 7.38 (dd, 1H), 7.21 (s, 1H), 7.04 (d, 1 H), 5.42 (s, 2 H), 4.29 (q, 2 H), 1.55 (s, 9 H), 1.29 (t, 3 H).

(5) **Step E: 4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97)**

101 (7.7 g, 16.3 mmol) is dissolved in 15 ml of a 1:1:1 mixture of THF / water / ethanol and after addition of KOH pellets (5.4 g, 81.9 mmol) the mixture is stirred for 2 h at 85°C. Then the organic phase is evaporated under reduced pressure. The residue is dissolved in ethyl acetate, acidified with 2M HCl and filtered off. The crude product is purified by crystallisation from ethyl acetate.
Yield: 4.4 g (79%) of white crystals. MS (ESI): 340 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.8 (s, 1H), 11.7 (s, 1H), 8.25 (s, 1H), 7.79 (d, 1H), 7.62 (d, 1H), 7.35 (dd, 1H), 7.15 (dd, 1H), 7.0 - 7.05 (m, 2H), 6.71 (d, 1H), 5.39 (s, 2H).

Example 43

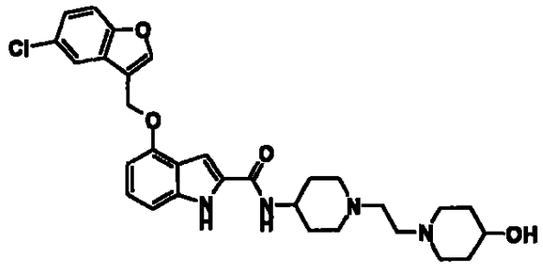
4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97, see example 42) and amine 5 analogously to the method described in example 1.
Yield: 52 mg (16%). MS (ESI): 549 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 10.98 (br s, 1H), 8.12 (s, 1H), 7.68 (d, 1H), 7.53 (d, 1H), 7.0 – 7.2 (m, 5H), 6.65 (d, 1H), 5.43 (s, 2H), 3.75 (m, 1H), 2.35 – 2.65 (m, 12H), 2.1 (m, 2H), 1.8 (m, 2H), 1.5 – 1.6 (m, 8H).

Example 44

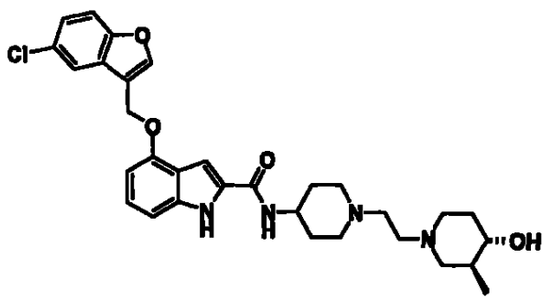
4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97, see example 42) and amine 21 analogously to the method described in example 1.
Yield: 50 mg (24%). MS (ESI): 551 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.22 (s, 1H), 8.12 (d, 1H), 7.78 (s, 1H), 7.67 (d, 1H), 7.37 (d, 1H), 7.18 (s, 1H), 7.08 (dd, 1H), 7.02 (d, 1H), 6.67 (m, 1H), 5.33 (s, 2H), 4.49 (b, 1H), 3.7 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.5 (m, 2H), 2.35 (m, 2H), 1.95 (m, 4H), 1.25 – 1.8 (m, 8H).

Example 45

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

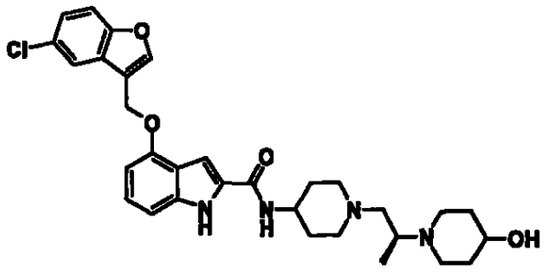


This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97, see example 42) and amine 14 analogously to the method described in example 1.

Yield: 85 mg (45%). MS (ESI): 565 $[M+H]^+$, 1H-NMR (120°C, DMSO-d_6): δ (ppm) 11.29 (br s, 1H), 8.2 (d, 1H), 8.1 (s, 1H), 7.74 (s, 1H), 7.57 (d, 1H), 7.34 (d, 1H), 7.22 (s, 1H), 7.09 (m, 1H), 6.72 (d, 1H), 5.39 (s, 2H), 2.6 – 4.1 (m, 15H), 1.75 – 2.2 (m, 6H), 1.00 (d, 3H).

Example 46

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

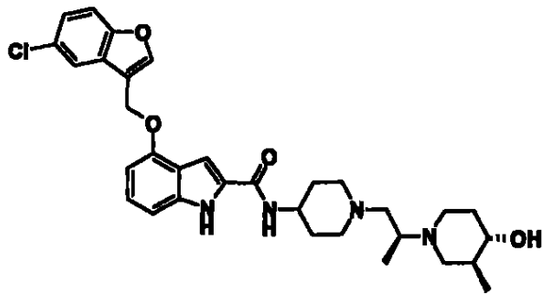


This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97, see example 42) and amine 50 analogously to the method described in example 1.

Yield: 125 mg (71%). MS (ESI): 565 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.3 – 10.7 (br, 2H), 8.52 (d, 1H), 8.24 (s, 1H), 7.75 (d, 1H), 7.68 (d, 1H), 7.35 (dd, 1H), 7.23 (s, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 2.7 – 3.7 (m, 12H), 1.7 – 2.1 (m, 8H), 1.35 / 1.3 (d, 3H) (rotamers).

Example 47

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

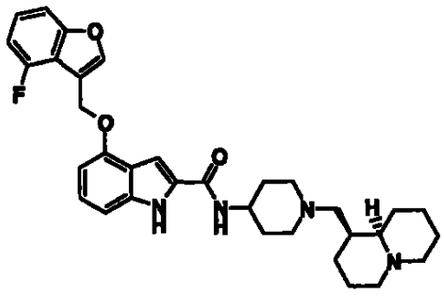


This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97, see example 42) and amine 56 analogously to the method described in example 1.

Yield: 123 mg (64%). MS (ESI): 579 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4 - 10.6 (br, 2H), 8.52 (d, 1H), 8.26 (s, 1H), 7.77 (d, 1H), 7.68 (d, 1H), 7.38 (dd, 1H), 7.23 (s, 1H), 7.12 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 2.8 – 3.9 (m, 13H), 1.9 – 2.1 (m, 6H), 1.31 (d, 3H), 0.94 (d, 3H).

Example 48

4-(4-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(4-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (104) (preparation see below) and amine 61 analogously to the method described in example 1.

Yield: 49 mg (22.5%). MS (ESI): 559.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5 (br d, 1H), 10.2 (br d, 1H), 8.45 (m, 1H), 8.25 (s, 1H), 7.5 (d, 1H), 7.38 (m, 1H), 7.25 (m, 1H), 7.1 (m, 2H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.0 (m, 1H), 2.8 – 3.6 (m, 14H), 1.3 – 2.1 (m, 12H).

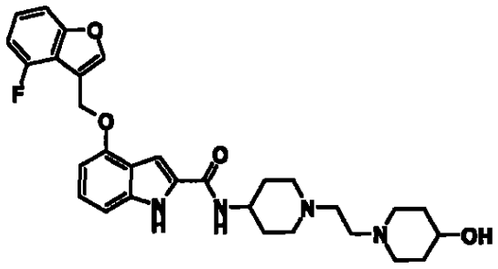
Synthesis of 4-(4-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (104):

This compound is synthesized from 2-fluoro-6-hydroxy-benzaldehyde analogously to the method described for 97 (see example 42).

Yield: 220 mg (49%) of white crystals. MS (ESI): 324.3 $[M-H]^-$.

Example 49

4-(4-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

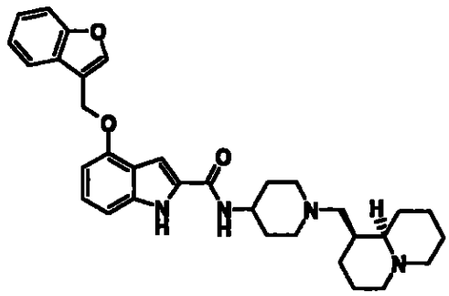


This compound is synthesized from 4-(4-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (104, see example 48) and amine 21 analogously to the method described in example 1.

Yield: 100 mg (61%). MS (ESI): 535 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 10.5 (br, 1H), 10.35 (br, 1H), 8.48 (d, 1H), 8.23 (m, 2H), 7.5 (d, 1H), 7.35 (m, 1H), 7.2 (s, 1H), 7.1 (m, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 2.9 – 3.75 (m, 13H), 1.65 – 2.1 (m, 8H).

Example 50

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (105) (preparation see below) and amine 61 analogously to the method described in example 1.

Yield: 68 mg (34%). MS (ESI): 541 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.56 (s, 1H), 10.5 (br d, 1H), 10.2 (br d, 1H), 8.5 (t, 1H), 8.18 (s, 1H), 7.72 (d, 1H), 7.6 (d, 1H), 7.25 – 7.35 (m, 3H), 7.12 (d, 1H), 7.03 (d, 1H), 6.75 (d, 1H), 5.57 (s, 2H), 4.01 (m, 1H), 2.8 – 3.6 (m, 14H), 1.3 – 2.1 (m, 12H).

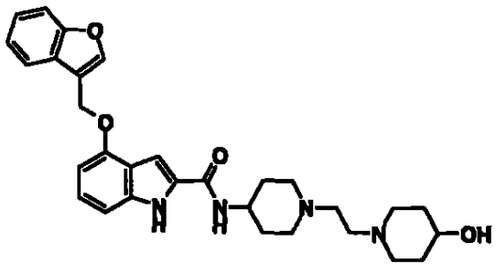
Synthesis of 4-(benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (105):

This compound is synthesized from 2-hydroxy-benzaldehyde analogously to the method described for 97 (see example 42).

MS (ESI): 306 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.7 (s, 1H), 8.15 (s, 1H), 7.73 (d, 1H), 7.58 (d, 1 H), 7.33 (dd, 1H), 7.29 (dd, 1H), 7.15 (dd, 1H), 7.05 (s, 1H), 7.02 (d, 1H), 6.73 (d, 1H), 5.38 (s, 2H).

Example 51

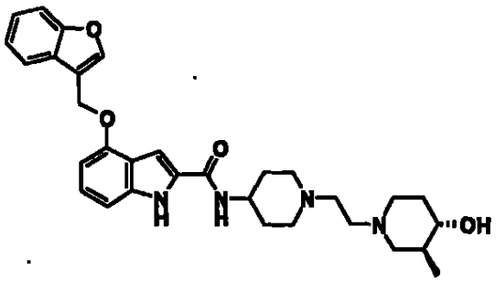
4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 105 (see example 50) and amine 21.
MS (ESI): 517.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.17 (s, 1H), 8.1 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.28 (d, 1H), 7.18 (s, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.48 (d, 1H), 3.71 (m, 1H), 3.39 (m, 1H), 2.84 (m, 2H), 2.69 (m, 2H), 2.35 (m, 4H) 1.98 (m, 4H), 1.69 (m, 4H), 1.48 (m, 2H), 1.34 (m, 2H).

Example 52

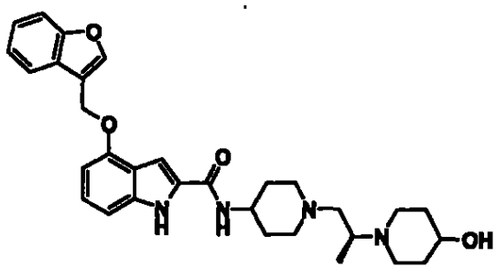
4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (105, see example 50) and amine 14.
MS (ESI): 531.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.17 (s, 1H), 8.11 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.19 (s, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (d, 2H), 4.47 (d, 1H), 3.7 (m, 1H), 3.3 (m, 1H), 2.85-2.91 (m, 5H), 2.34 (m, 4H), 1.83-2.04 (m, 3H), 1.65-1.77 (m, 3H), 1.27-1.63 (m, 5H), 0.85 (d, 3H).

Example 53

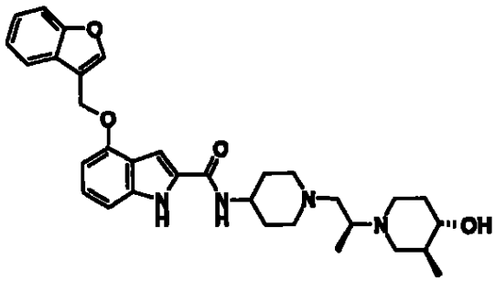
4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 105 (see example 50) and amine 50.
MS (ESI): 531.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.17 (s, 1H), 8.11 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.19 (d, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.44 (d, 1H), 3.7 (br m, 1H), 3.35 (m, 1H), 2.97 (m, 1H), 2.6-2.9 (m, 4H), 2.0-2.35 (m, 4H), 1.89 (m, 1H), 1.63-1.77 (m, 3H), 1.4-1.6 (m, 3H), 1.2-1.38 (m, 3H), 0.90 (d, 3H).

Example 54

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

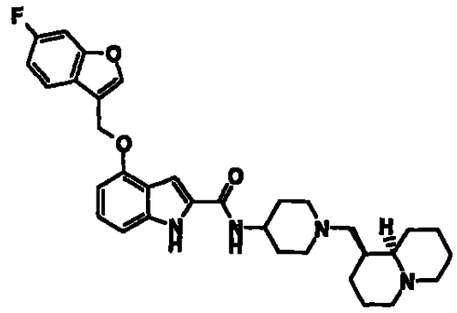


This compound is synthesized analogously to example 1 from 4-(benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 105 (see example 50) and amine 56.

MS (ESI): 545.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.17 (s, 1H), 8.11 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.19 (s, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.43 (d, 1H), 3.71(m, 1H), 2.59-2.92 (m, 6H), 2.31 (m, 1H), 2.22 (m, 1H), 2.01-2.17 (m, 2H), 1.88 (m, 2H), 1.66-1.76 (m, 3H), 1.2-1.58 (m, 4H), 0.89 (d, 3H), 0.86 (d, 3H).

Example 55

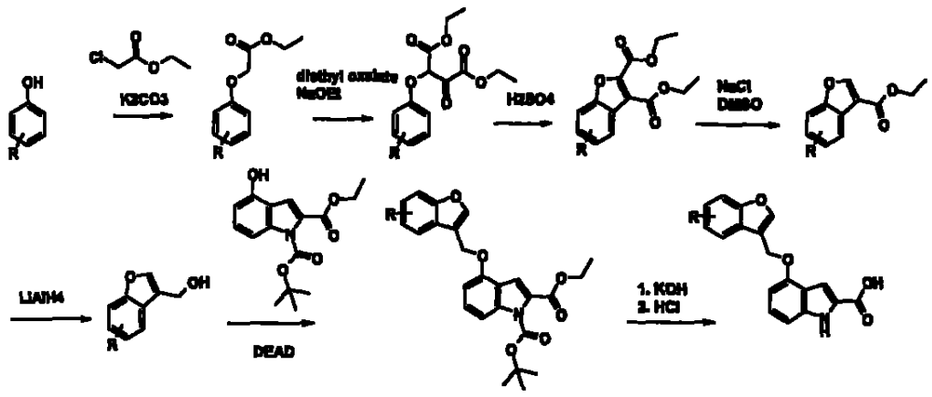
4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(6-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (106) (preparation see below) and amine 61 analogously to the method described in example 1.

Yield: 80 mg (41.2%). MS (ESI): 559 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.63 (br d, 1H), 10.35 (br d, 1H), 8.5 (m, 1H), 8.2 (s, 1H), 7.72 (dd, 1H), 7.58 (dd, 1H), 7.25 (m, 1H), 7.2 (m, 1H), 7.1 (d, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.6 – 3.6 (m, 14H), 1.3 – 2.1 (m, 12H).

Reaction Scheme 14:



Synthesis of 4-(6-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (106):

(1) Step A: (3-Fluoro-phenoxy)-acetic acid ethyl ester (107)

3-Fluoro-phenol (100 g, 892 mmol) is dissolved in acetone (250 ml) and after addition of chloro-acetic acid ethyl ester (114 ml, 1.07 mol) and K2CO3 (249 g, 1.78 mol) the mixture is refluxed for 24h. After cooling down to 0°C, the mixture is filtrated and the filtrate is evaporated under reduced pressure. Yield: 198 g (100%) of a red oil.

(2) Step B: 2-(3-Fluoro-phenoxy)-3-oxo-succinic acid diethyl ester (108)

60% NaH in mineral oil (19.5 g, 486.4 mmol) is covered with 600 ml of dry diethyl ether. Ethanol (28.1 ml, 444 mmol) is added dropwise within 25 min. Then oxalic acid diethyl ester (66 ml, 488 mmol) is added dropwise within 20 min. After 10 min stirring at room temperature, the mixture is heated to reflux. A solution of 107 (88g, 444 mmol) in 80 ml of dry diethyl ether is added dropwise within 30 min and the mixture is allowed to reflux for 1 hour. After cooling down to room temperature, the reaction mixture is poured on 2M HCl (400 ml) / ice (400 g) and extracted with diethyl ether. The organic layers are dried over sodium sulfate, filtatrated and evaporated. The crude product is purified by filtration over silica gel (ethyl acetate / hexane 1:1). Evaporation gave 140 g of an red oil. The mineral oil could be removed using a separatoty funnel. Yield: 132 g (100%).

(3) Step C: 6-Fluoro-benzofuran-2,3-dicarboxylic acid diethyl ester (109)

108 (66 g, 221.3 mmol) is dissolved in 245 ml of cooled (-15°C) conc. sulfuric acid and stirred for 3 h whereas the reaction mixture slowly warmed up to room temperature. Then the mixture is poured onto 1 kg of ice and extracted with diethyl ether. The organic layers are washed with brine, dried over sodium sulfate, filtrated and evaporated. The crude product is used in the next step without further purification.
Yield: 19.7 g (32%) of a yellow oil. MS (ESI): 281 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.88 (dd, 1H), 7.82 (dd, 1H), 7.35 (ddd, 1H), 4.38 (m, 4H), 1.33 (t, 3H), 1.32 (t, 6H). The cyclisation gave exclusively the 6-substituted benzofurane.

(4) Step D: 6-Fluoro-benzofuran-3-carboxylic acid ethyl ester (110)

109 (40 g, 142.7 mmol) is dissolved in 300 ml of a DMSO and after addition of sodium chloride (16.7 g, 285.4 mmol) and water (5.1 ml) the mixture is stirred for 4h at 160°C (temperature of reaction mixture). Then the mixture is allowed to cool down and evaporated at high vacuum. The residue is dissolved in ethyl acetate, washed with water and brine and dried over sodium sulfate. Evaporation gave 14.6 g of an red oil, which is further purified by filtration over silica gel (ethyl acetate / hexanes 2:8).
Yield: 7.8 g (26%) of a yellow solid. MS (ESI): 208 $[M]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.77 (s, 1H), 7.92 (dd, 1H), 7.68 (dd, 1H), 7.29 (ddd, 1H), 4.35 (q, 2H), 1.32 (t, 3H).

(5) Step E: (6-Fluoro-benzofuran-3-yl)-methanol (111)

1M LiAlH4-solution in THF (75.9 ml, 75.9 mmol) is diluted with 100 ml of THF and cooled to 0°C. 110 (7.9 g, 37.9 mmol) is dissolved in 100 ml of THF and added dropwise within 30 min. After completed addition the mixture is allowed to stir at rt for 2h. Then the reaction mixture is cooled to -15°C and 10 ml of a 1M NaOH solution is added very slowly. The the mixture is filtrated over celite and evaporation under reduced pressure gave 5.3 g of a yellow oil.

(6) Step F: 4-(6-Fluoro-benzofuran-3-ylmethoxy)-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (112)

111 (2 g, 12 mmol), 102 (3.7 g, 12 mmol), triphenylphosphine (9.4 g, 36.1 mmol) and DIPEA (6.2 ml, 36.1 mmol) are dissolved in 50 ml of THF and cooled to 0°C. Then 40% ethyl azodicarboxylate solution in THF (15.7 ml, 36.1 mmol) is added dropwise. After completed

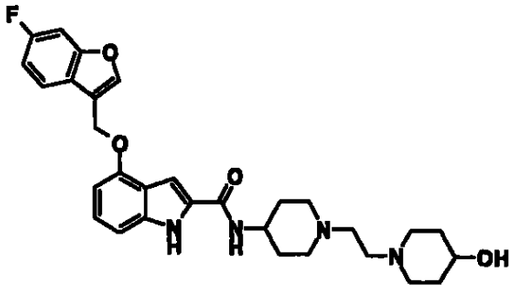
addition the mixture is stirred for 16h (TLC control) at rt. Then the mixture is evaporated under reduced pressure. The residue is diluted with ethyl acetate, washed sat. NaHCO3- and NaCl-solution, and dried over Na2SO4. The crude product is purified by Flash-chromatography (ethyl acetate / hexanes (1:9), silicagel).
Yield: 1.2 g (22%) of a red oil. MS (ESI): 454 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.22 (s, 1H), 7.73 (dd, 1H), 7.58 (dd, 1H), 7.53 (d, 1H), 7.38 - 7.40 (m, 2H), 7.15 – 7.7.25 (m, 1H), 7.05 (d, 1 H), 5.43 (s, 2 H), 4.05 (q, 2 H), 1.55 (s, 9 H), 1.29 (t, 3 H).

(7) **Step G: 4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (108)**

112 (1.2 g, 2.6 mmol) is dissolved in 30 ml of a 1:1:1 mixture of THF, ethanol and water. And after addition of KOH pellets (742 mg, 13.2 mmol) the mixture is stirred for 2h (TLC control) at 85°C. Then the organic solvent are removed under reduced pressure. The residue is cooled to 0°C and treated with 2M HCl. The crude product is filtered off and dried under high vacuum. The crude product (800mg) is recrystallized from ethl acetate.
Yield: 520 mg (60%) of colorless crystals. MS (ESI): 324 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.7 (s, 1H), 8.18 (s, 1H), 7.73 (dd, 1H), 7.57 (dd, 1 H), 7.18 (dd, 1H), 7.15 (d, 1H), 7.05 (s, 1H), 7.02 (d, 1H), 6.72 (d, 1H), 5.38 (s, 2H).

Example 58

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

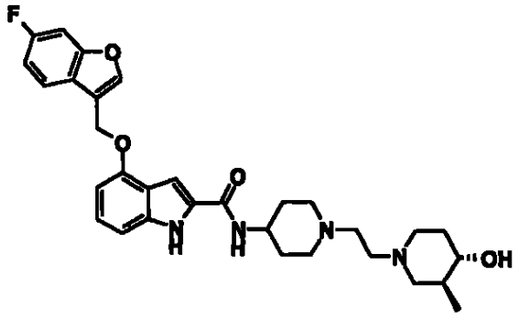


This compound is synthesized from 4-(6-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (106, see example 55) and amine 21 analogously to the method described in example 1.

Yield: 70 mg (38%). MS (ESI): 535 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.55 (br, 1H), 10.45 (br, 1H), 8.5 (br d, 1H), 8.2 (s, 1H), 7.7 (dd, 1H), 7.6 (dd, 2H), 7.15 - 7.25 (m, 2H), 7.1 (dd, 1H), 7.03 (d, 1H), 5.35 (s, 2H), 5.0 (br, 1H), 4.05 (m, 1H), 2.9 – 3.7 (m, 13H), 1.7 – 2.1 (m, 8H).

Example 57

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

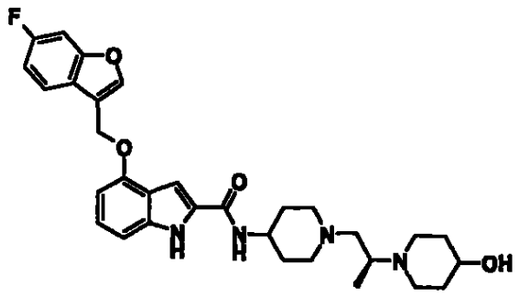


This compound is synthesized from 4-(6-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (106, see example 55) and amine 14 analogously to the method described in example 1.

Yield: 135 mg (71%). MS (ESI): 549 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.65 (br, 2H), 8.52 (d, 1H), 8.2 (s, 1H), 7.72 (dd, 1H), 7.58 (dd, 1H), 7.24 (s, 1H), 7.2 (m, 1H), 7.1 (dd, 1H), 7.04 (d, 1H), 6.72 (d, 1H), 5.35 (s, 2H), 2.6 – 4.2 (m, 14H), 1.75 – 2.2 (m, 8H), 0.93 (d, 3H).

Example 58

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

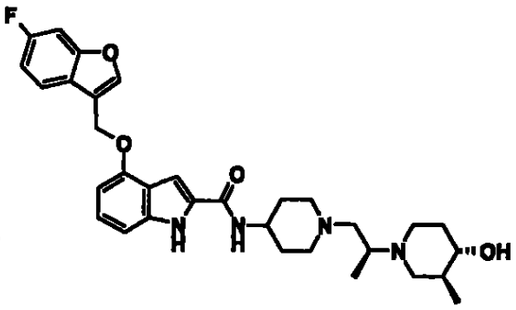


This compound is synthesized from 4-(6-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (106, see example 55) and amine 50 analogously to the method described in example 1.

Yield: 75 mg (39%). MS (ESI): 549 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.3 – 10.7 (br, 2H), 8.53 (d, 1H), 8.2 (s, 1H), 7.72 (dd, 1H), 7.58 (dd, 1H), 7.24 (s, 1H), 7.2 (m, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 5.1 (br, 1H), 2.8 – 4.1 (m, 13H), 1.7 – 2.2 (m, 8H), 1.35 / 1.3 (d, 3H) (rotamers).

Example 59

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



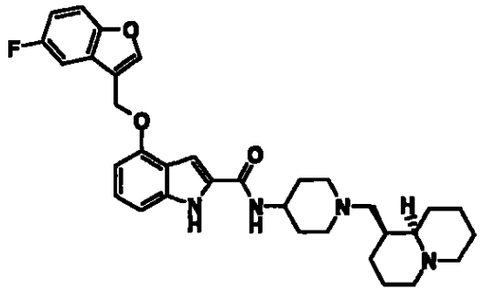
This compound is synthesized analogously to example 1 from 4-(6-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 108 (see example 55) and amine 56.

MS (ESI): 463.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.19 (s, 1H), 8.11 (d, 1H), 7.71 (dd, 1H), 7.58 (dd, 1H), 7.19 (m, 2H), 7.09 (t, 1H), 7.01 (d, 1H), 6.7 (d, 1H), 5.34 (s, 2H), 4.43 (d, 1H), 3.71 (m, 1H), 2.58-2.92 (m, 6H), 2.31 (m, 1H), 2.22 (m, 1H), 2.02-2.18

(m, 2H), 1.89 (m, 2H), 1.64-1.78 (m, 3H), 1.42-1.59 (m, 2H), 1.2-1.4 (m, 2H), 0.9 (d, 3H), 0.86 (d, 3H).

Example 60

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (113) (preparation see below) and amine 61 analogously to the method described in example 1.

Yield: 840 mg (72.5%). MS (ESI): 559 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.23 (s, 1H), 8.1 (d, 1H), 7.84 (dd, 1H), 7.48 (dd, 1H), 7.17 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.68 (d, 1H), 5.35 (s, 2H), 3.75 (m, 1H), 2.65 – 2.85 (m, 4H), 2.47 (m, 1H), 2.25 (dd, 1H), 1.2 – 2.05 (m, 20H).

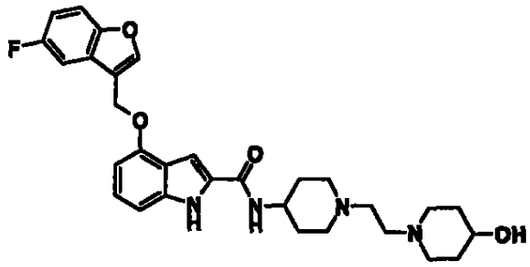
Synthesis of 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (113):

This compound is synthesized from 4-fluoro-phenol analogously to the method described for 106 (see example 55).

MS (ESI): 324.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.81 (br s, 1H), 11.7 (s, 1H), 8.24 (s, 1H), 7.64 (dd, 1H), 7.51 (dd, 1 H), 7.15 (m, 2H), 7.05 (m, 2H), 6.7 (d, 1H), 5.37 (s, 2H).

Example 61

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

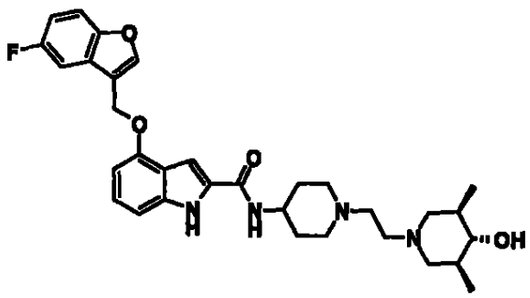


This compound is synthesized from 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (113, see example 60) and amine 21 analogously to the method described in example 1.

Yield: 160 mg (57%). MS (ESI): 535 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.65 (br, 1H), 10.55 (br, 1H), 8.51 (br d, 1H), 8.25 (s, 1H), 7.65 (m, 1H), 7.45 (dd, 2H), 7.2 (s, 1H), 7.05 – 7.15 (m, 3H), 6.7 (d, 1H), 5.35 (s, 2H), 4.12 (m, 1H), 3.84 (m, 1H), 2.9 – 3.7 (m, 13H), 1.75 – 2.2 (m, 8H).

Example 62

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3R,4R,5S)-4-hydroxy-3,5-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

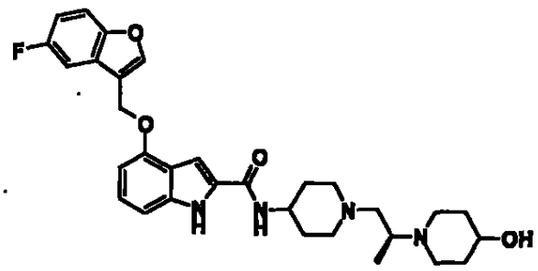


This compound is synthesized from 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (113, see example 60) and amine 41 analogously to the method described in example 1.

Yield: 110 mg (56%). MS (ESI): 563 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5 - 10.7 (br, 2H), 8.5 (d, 1H), 8.22 (s, 1H), 7.63 (dd, 1H), 7.49 (dd, 1H), 7.2 (m, 2H), 7.1 (d, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.32 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 2.6 – 3.8 (m, 13H), 1.8 – 2.1 (m, 6H), 0.93 (d, 6H).

Example 63

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

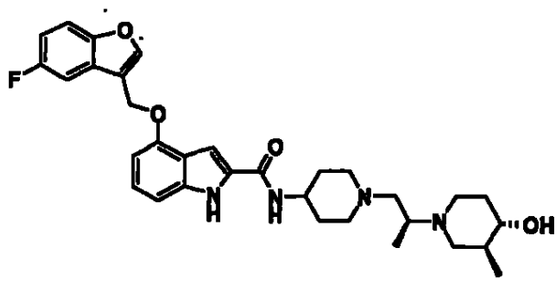


This compound is synthesized from 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (113, see example 60) and amine 60 analogously to the method described in example 1.

Yield: 85 mg (45%). MS (ESI): 549 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.2 – 10.6 (br, 2H), 8.5 (d, 1H), 8.24 (s, 1H), 7.65 (dd, 1H), 7.5 (m, 1H), 7.15 – 7.3 (m, 2H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 5.04 (br, 1H), 2.8 – 4.1 (m, 13H), 1.7 – 2.2 (m, 8H), 1.35 / 1.3 (d, 3H) (rotamers).

Example 64

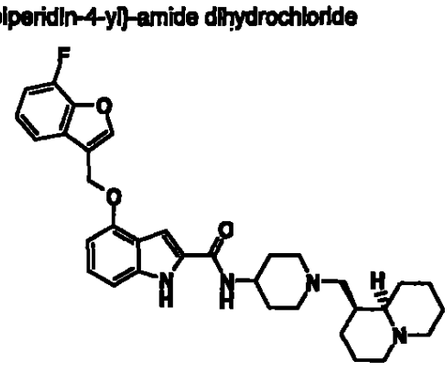
4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 113 (see example 60) and amine 58.
MS (ESI): 563.1 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.95 (s, 1H), 7.48 (dd, 1H), 7.43 (dd, 1H), 7.21 (s, 1H), 7.15 (t, 1H), 7.02-7.12 (m, 2H), 6.69 (d, 1H), 5.34 (s, 2H), 3.86 (m, 1H), 2.72-3.12 (m, 6H), 2.51 (m, 1H), 2.17-2.41 (m, 3H), 1.97-2.15 (m, 2H), 1.81-1.96 (m, 3H), 1.45-1.76 (m, 4H), 1.05 (d, 3H), 0.98 (d, 3H).

Example 65

4-(7-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



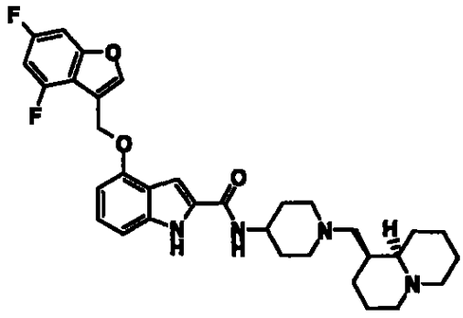
This compound is synthesized from 4-(7-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (114) (preparation see below) and amine 61 analogously to the method described in example 1.
Yield: 194 mg (40%). MS (ESI): 559 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.2 – 10.7 (br, 2H), 8.45 (dd, 1H), 8.28 (s, 1H), 7.58 (dd, 1H), 7.2 – 7.3 (m, 3H), 7.1 (m, 1H), 7.05 (d, 1H), 6.72 (d, 1H), 5.38 (s, 2H), 4.0 (m, 1H), 2.65 – 2.85 (m, 6H), 1.2 – 2.05 (m, 20H).

Synthesis of 4-(7-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (114):

This compound is synthesized from 2-fluoro-phenol analogously to the method described for 106 (see example 55).
MS (ESI): 324.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.85 (br s, 1H), 11.75 (s, 1H), 8.25 (s, 1H), 7.58 (dd, 1H), 7.2 – 7.3 (m, 2 H), 7.15 (dd, 1H), 7.05 (s, 1H), 7.02 (d, 1H), 6.72 (d, 1H), 5.4 (s, 2H).

Example 66

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



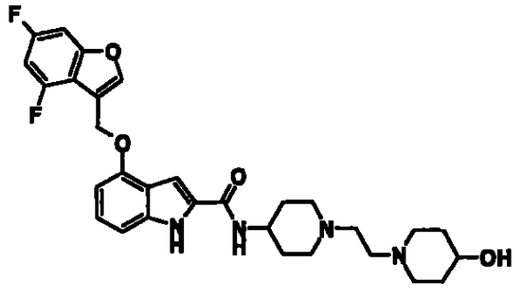
This compound is synthesized from 4-(4,6-difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (115) (preparation see below) and amine 61 analogously to the method described in example 1.
Yield: 155 mg (82%). MS (ESI): 577 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5 (br d, 1H), 10.2 (br d, 1H), 8.45 (br d, 1H), 8.25 (s, 1H), 7.55 (d, 1H), 7.2 – 7.25 (m, 2H), 7.1 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.0 (m, 1H), 2.8 – 3.6 (m, 14H), 1.3 – 2.1 (m, 12H).

Synthesis of 4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (115):

This compound is synthesized from 3,5-difluoro-phenol analogously to the method described for 106 (see example 55).
MS (ESI): 342 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.6 (s, 1H), 8.24 (s, 1H), 7.51 (dd, 1H), 7.2 (ddd, 1 H), 7.15 (dd, 1H), 7.04 (d, 1H), 7.02 (s, 1H), 6.7 (d, 1H), 5.32 (s, 2H).

Example 67

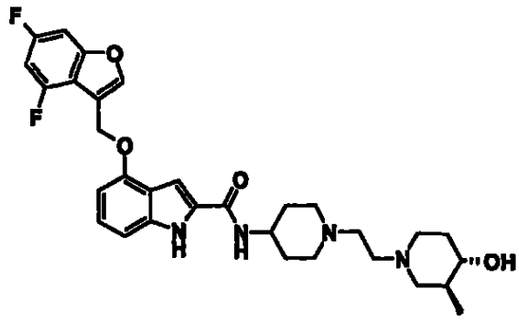
4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(4,6-difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (115, see example 66)) and amine 21 analogously to the method described in example 1.
Yield: 90 mg (49%). MS (ESI): 553 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5 (br, 1H), 10.35 (br, 1H), 8.48 (br d, 1H), 8.25 (s, 1H), 7.54 (d, 1H), 7.2 (m, 2H), 7.12 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 4.07 (m, 1H), 2.9 – 3.75 (m, 13H), 1.65 – 2.1 (m, 8H).

Example 68

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

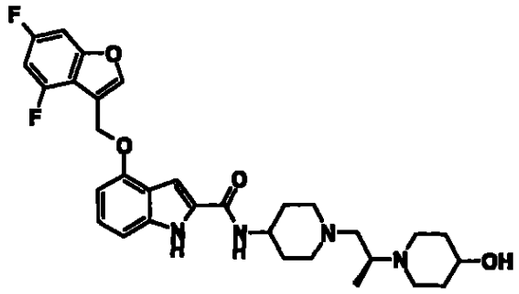


This compound is synthesized from 4-(4,6-difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (115, see example 66) and amine 14 analogously to the method described in example 1.

Yield: 125 mg (67%). MS (ESI): 567 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.65 (br, 2H), 8.5 (d, 1H), 8.25 (s, 1H), 7.53 (dd, 1H), 7.2 – 7.3 (m, 2H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 2.6 – 4.1 (m, 14H), 1.75 – 2.2 (m, 8H), 0.93 (d, 3H).

Example 69

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

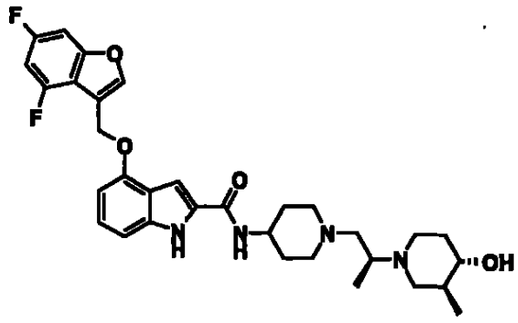


This compound is synthesized from 4-(4,6-difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (115, see example 66) and amine 50 analogously to the method described in example 1.

Yield: 105 mg (56%). MS (ESI): 567 $[M+H]^+$, 1H-NMR (120°C, DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.3 – 10.7 (br, 2H), 8.52 (d, 1H), 8.26 (s, 1H), 7.53 (d, 1H), 7.2 (m, 2H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 2.9 – 3.9 (m, 12H), 1.7 – 2.2 (m, 8H), 1.34 (d, 3H).

Example 70

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

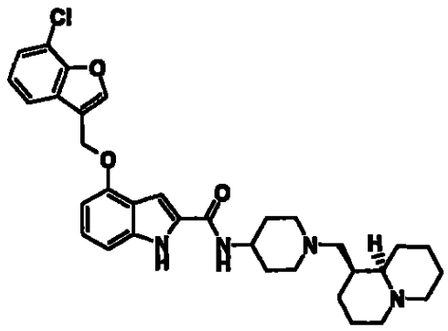


This compound is synthesized from 4-(4,6-difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (115, see example 66) and amine 56 analogously to the method described in example 1.

Yield: 130 mg (68%). MS (ESI): 581 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4 - 10.6 (br, 2H), 8.5 (d, 1H), 8.27 (s, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 2.8 – 3.9 (m, 13H), 1.9 – 2.1 (m, 6H), 1.3 (d, 3H), 0.93 (d, 3H).

Example 71

4-(7-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(7-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (116) (preparation see below) and amine 61 analogously to the method described in example 1.

Yield: 55 mg (29%). MS (ESI): 575 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.1 – 10.6 (br, 2H), 8.5 (dd, 1H), 8.3 (s, 1H), 7.7 (d, 1H), 7.48 (d, 1H), 7.32 (dd, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 5.38 (s, 2H), 4.0 (m, 1H), 2.65 – 2.85 (m, 6H), 1.2 – 2.05 (m, 20H).

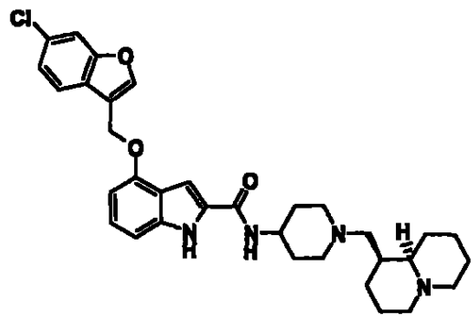
Synthesis of 4-(7-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (116):

This compound is synthesized from 2-chloro-phenol analogously to the method described for 106 (see example 55).

MS (ESI): 340 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 10.86 (s, 1H), 8.25 (s, 1H), 7.71 (d, 1H), 7.42 (d, 1 H), 7.30 (dd, 1H), 6.93 (m, 2H), 6.58 (d, 1H), 6.34 (s, 1H), 5.36 (s, 2H) (potassium salt).

Example 72

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(6-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (117) (preparation see below) and amine 61 analogously to the method described in example 1.

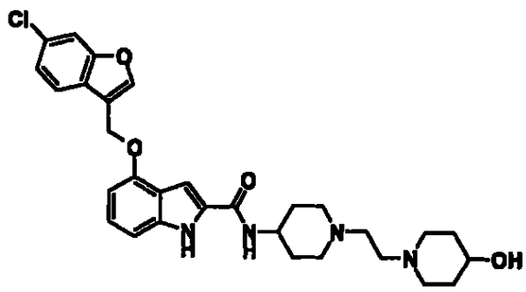
Yield: 85 mg (49.8%). MS (ESI): 575 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br d, 1H), 10.3 (br d, 1H), 8.49 (br dd, 1H), 8.22 (s, 1H), 7.8 (d, 1H), 7.72 (d, 1H), 7.38 (dd, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.8 – 3.8 (m, 14H), 1.3 – 2.1 (m, 12H).

Synthesis of 4-(6-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (117):

This compound is synthesized from 3-chloro-phenol analogously to the method described for 106 (see example 55). The cyclisation with concentrated sulphuric acid (Step C) gave a 1:1 mixture of the 4- and 6-substituted benzofuranes, which could be separated in step D. MS (ESI): 340 [M-H].

Example 73

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

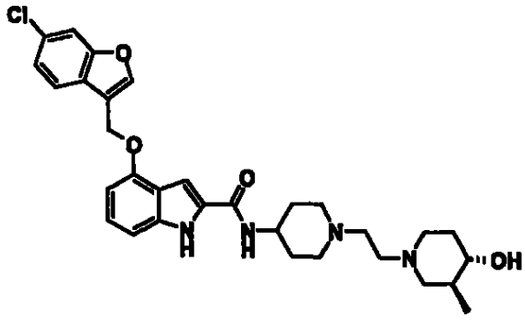


This compound is synthesized from 4-(6-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (117, see example 72) and amine 21 analogously to the method described in example 1.

Yield: 63 mg (34%). MS (ESI): 551 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.22 (s, 1H), 8.15 (br d, 1H), 7.81 (s, 1H), 7.75 (d, 1H), 7.35 (dd, 1H), 7.18 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.75 (b, 1H), 2.1 – 3.9 (m, 14H), 1.4 – 1.8 (m, 8H).

Example 74

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

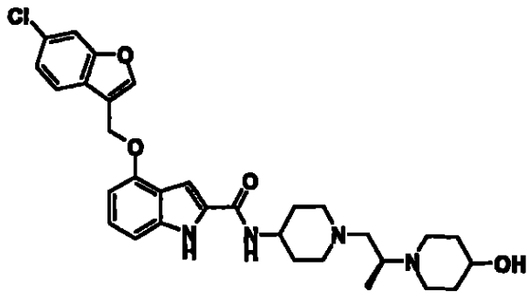


This compound is synthesized from 4-(6-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (117, see example 72) and amine 14 analogously to the method described in example 1.

Yield: 55 mg (32%). MS (ESI): 565 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.5 (br, 2H), 8.48 (d, 1H), 8.22 (s, 1H), 7.80 (s, 1H), 7.70 (d, 1H), 7.37 (d, 1H), 7.22 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.71 (d, 1H), 5.34 (s, 2H), 2.6 – 4.2 (m, 14H), 1.75 – 2.2 (m, 8H), 0.93 (d, 3H).

Example 75

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

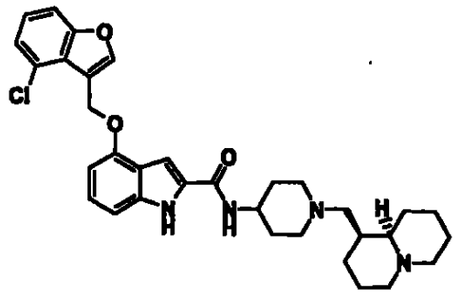


This compound is synthesized from 4-(6-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (117, see example 72) and amine 50 analogously to the method described in example 1.

Yield: 85 mg (46%). MS (ESI): 565 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.2 – 10.6 (br, 2H), 8.5 (d, 1H), 8.21 (s, 1H), 7.8 (d, 1H), 7.7 (d, 1H), 7.35 (dd, 1H), 7.24 (s, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 5.0 (br, 1H), 2.85 – 4.2 (m, 13H), 1.7 – 2.2 (m, 8H), 1.35 / 1.3 (d, 3H) (rotamers).

Example 76

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



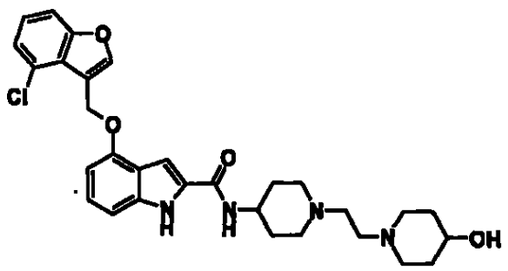
This compound is synthesized from 4-(4-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (118) (preparation see below) and amine 61 analogously to the method described in example 1.
Yield: 230 mg (58.8%). MS (ESI): 575 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br d, 1H), 10.3 (br d, 1H), 8.45 (br dd, 1H), 8.3 (s, 1H), 7.65 (dd, 1H), 7.3 – 7.4 (m, 2H), 7.25 (m, 1H), 7.1 (m, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.6 – 3.6 (m, 14H), 1.3 – 2.1 (m, 12H).

Synthesis of 4-(4-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (118):

This compound is synthesized from 3-chloro-phenol analogously to the method described for 106 (see example 55). The cyclisation with concentrated sulphuric acid (Step C) gave a 1:1 mixture of the 4- and 6-substituted benzofuranes, which could be separated in step D.
MS (ESI): 340 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.75 (br s, 1H), 11.7 (s, 1H), 8.31 (s, 1H), 7.6 (dd, 1H), 7.35 (m, 2 H), 7.15 (dd, 1H), 7.02 (m, 2H), 6.75 (d, 1H), 5.42 (s, 2H).

Example 77

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

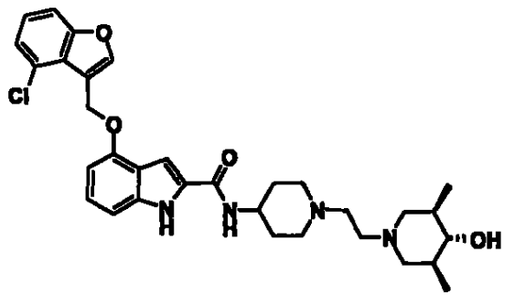


This compound is synthesized from 4-(4-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (118, see example 76) and amine 21 analogously to the method described in example 1.
Yield: 160 mg (99%). MS (ESI): 551 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.52 (s, 1H), 10.35 (br, 1H), 10.2 (br, 1H), 8.5 (br, 1H), 8.31 (s, 1H), 7.63 (d, 1H), 7.36 (m, 2H), 7.22 (s,

1H), 7.11 (dd, 1H), 7.03 (d, 1H), 6.71 (d, 1H), 5.37 (s, 2H), 5.02 (br, 1H), 4.05 (m, 1H), 2.9 – 3.75 (m, 13H), 1.65 – 2.1 (m, 8H).

Example 78

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3R,4R,5S)-4-hydroxy-3,5-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

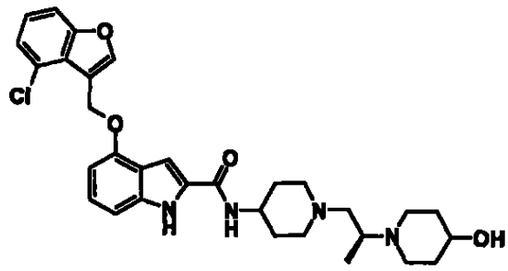


This compound is synthesized from 4-(4-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (118, see example 76) and amine 41 analogously to the method described in example 1.

Yield: 45 mg (39%). MS (ESI): 577 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.45 - 10.7 (br, 2H), 8.47 (d, 1H), 8.32 (s, 1H), 7.65 (d, 1H), 7.35 (m, 2H), 7.21 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 5.0 (br, 1H), 4.05 (m, 1H), 2.6 – 3.8 (m, 13H), 1.8 – 2.1 (m, 6H), 0.93 (d, 6H).

Example 79

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

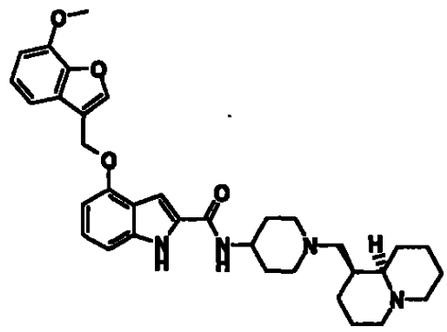


This compound is synthesized from 4-(4-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (118, see example 76) and amine 60 analogously to the method described in example 1.

Yield: 20 mg (13%). MS (ESI): 565 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.3 (s, 1H), 8.1 (d, 1H), 7.62 (d, 1H), 7.35 (m, 2H), 7.2 (s, 1H), 7.1 (dd, 1H), 7.0 (d, 1H), 6.7 (d, 1H), 5.4 (s, 2H), 4.5 (br, 1H), 4.05 (m, 1H), 3.7 (m, 1H), 2.6 – 2.9 (m, 4H), 1.1 – 2.4 (m, 15H), 0.9 (d, 3H).

Example 80

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



This compound is synthesized from 4-(7-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (119) (preparation see below) and amine 61 analogously to the method described in example 1.

Yield: 130 mg (68.1%). MS (ESI): 571 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.6 (br d, 1H), 10.2 (br d, 1H), 8.47 (dd, 1H), 8.13 (s, 1H), 7.25 (m, 2H), 7.2 (dd, 1H), 7.09

(d, 1H), 7.02 (d, 1H), 6.95 (d, 1H), 6.72 (d, 1H), 5.32 (s, 2H), 4.0 (m, 1H), 3.83 (s, 3H), 2.8 – 3.8 (m, 14H), 1.3 – 2.1 (m, 12H).

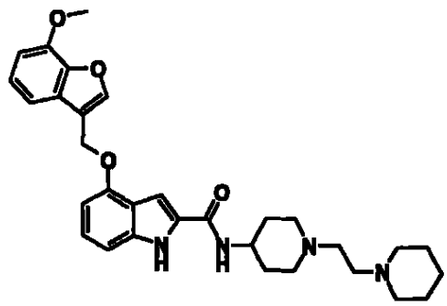
Synthesis of 4-(7-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (119):

This compound is synthesized from 2-methoxy-phenol analogously to the method described for 106 (see example 55).

MS (ESI): 336 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.54 (br s, 1H), 8.11 (s, 1H), 7.28 (d, 1H), 7.18 (dd, 1H), 7.09 (m, 1H), 7.0 (d, 1H), 6.95 (d, 1H), 6.92 m, 1H), 6.70 (d, 1H), 5.35 (s, 2H), 3.92 (s, 3H).

Example 81

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

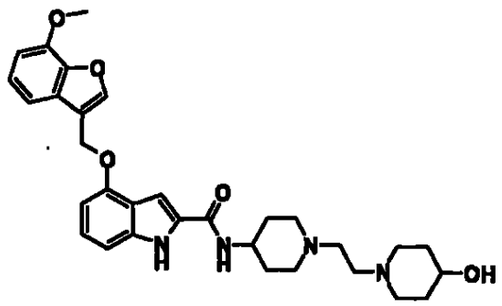


This compound is synthesized from 4-(7-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (119, see example 80) and amine 1 analogously to the method described in example 1.

Yield: 162 mg (48%). MS (ESI): 531 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.53 (s, 1H), 10.55 (br, 1H), 10.31 (br, 1H), 8.49 (d, 1H), 8.12 (s, 1H), 7.25 (dd, 1H), 7.22 (br s, 1H), 7.19 (dd, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 7.95 (d, 1H), 6.7 (d, 1H), 5.31 (s, 2H), 4.05 (m, 1H), 3.93 (s, 3H), 3.5 – 3.8 (m, 8H), 3.1 (m, 2H), 2.9 (m, 2H), 1.7 – 2.1 (m, 8H), 1.4 (m, 2H).

Example 82

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

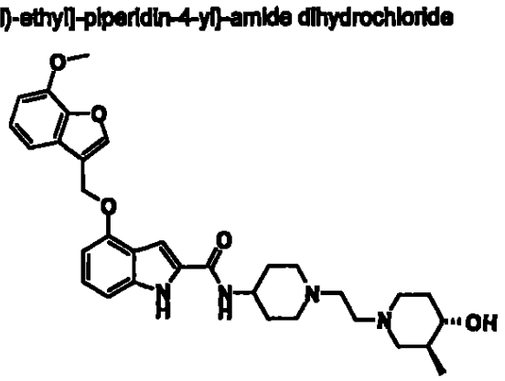


This compound is synthesized from 4-(7-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (119, see example 80) and amine 21 analogously to the method described in example 1.

Yield: 135 mg (73%). MS (ESI): 547 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 10.5 (br, 1H), 10.4 (br, 1H), 8.5 (br, 1H), 8.14 (s, 1H), 7.2 – 7.3 (m, 3H), 7.1 (dd, 1H), 7.0 (d, 1H), 6.95 (d, 1H), 6.7 (d, 1H), 5.32 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 3.93 (s, 3H), 2.7 – 3.7 (m, 13H), 1.6 – 2.1 (m, 8H).

Example 83

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

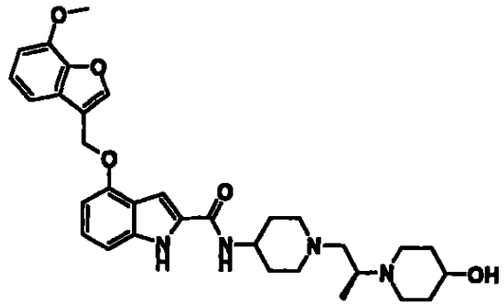


This compound is synthesized from 4-(7-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (119, see example 80) and amine 14 analogously to the method described in example 1.

Yield: 100 mg (53%). MS (ESI): 561 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 8.13 (s, 1H), 7.18 – 7.3 (m, 3H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.96 (d, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 3.95 (s, 3H), 2.6 – 4.2 (m, 14H), 1.75 – 2.2 (m, 8H), 0.93 (d, 3H).

Example 84

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

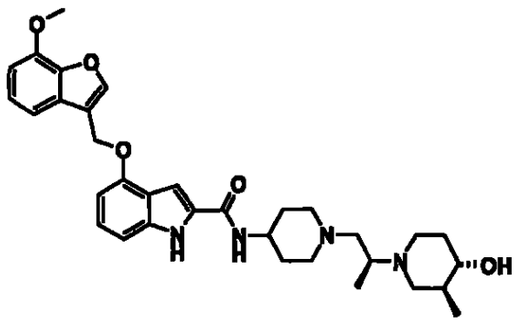


This compound is synthesized from 4-(7-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (119, see example 80) and amine 50 analogously to the method described in example 1.

Yield: 166 mg (94%). MS (ESI): 561 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.2 – 10.6 (br, 2H), 8.5 (d, 1H), 8.14 (s, 1H), 7.28 (d, 1H), 7.23 (s, 1H), 7.2 (dd, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.95 (d, 1H), 6.7 (d, 1H), 5.33 (s, 2H), 5.05 (br, 1H), 3.93 (s, 3H), 2.9 – 4.1 (m, 13H), 1.7 – 2.2 (m, 8H), 1.35 / 1.3 (d, 3H) (rotamers).

Example 85

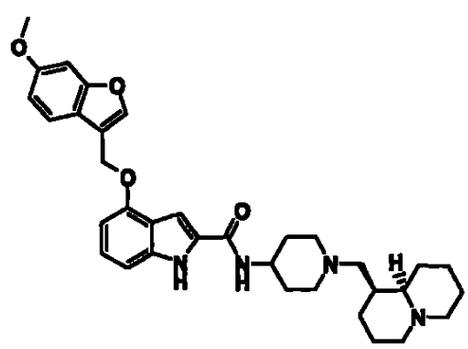
4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(7-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 119 (see example 80) and amine 56.
MS (ESI): 575.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.49 (s, 1H), 8.15 (s, 1H), 8.13 (d, 1H), 7.26 (d, 1H), 7.22 (t, 1H), 7.2 (s, 1H), 7.1 (t, 1H), 7.02 (d, 1H), 6.97 (d, 1H), 6.71 (d, 1H), 5.34 (s, 2H), 4.43 (d, 1H), 3.95 (s, 3H), 3.72 (m, 1H), 2.6-2.93 (m, 6H), 2.31 (m, 1H), 2.23 (m, 1H), 2.03-2.17 (m, 2H), 1.89 (m, 2H), 1.66-1.77 (m, 3H), 1.42-1.58 (m, 2H), 1.2-1.4 (m, 2H), 0.89 (d, 3H), 0.85 (d, 3H).

Example 86

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(6-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (120) (preparation see below) and amine 61 analogously to the method described in example 1.

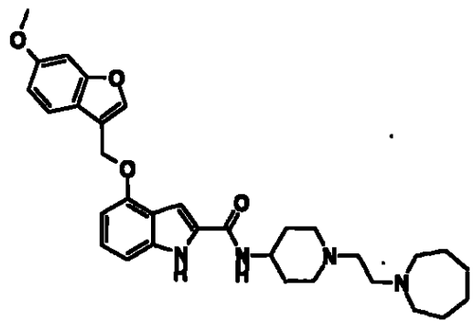
Yield: 108 mg (63.8%). MS (ESI): 571 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.1 (d, 1H), 8.03 (s, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.93 (dd, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 3.76 (s, 3H), 3.73 (m, 1H), 2.65 – 2.85 (m, 4H), 2.47 (m, 1H), 2.25 (dd, 1H), 1.2 – 2.05 (m, 20H).

Synthesis of 4-(6-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (120):

This compound is synthesized from 3-methoxy-phenol analogously to the method described for 106 (see example 55). The cyclisation with concentrated sulphuric acid (Step C) gave exclusively the 6-substituted benzofurane.
MS (ESI): 336 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.81 (br s, 1H), 11.71 (s, 1H), 8.02 (s, 1H), 7.56 (d, 1H), 7.18 (s, 1H), 7.13 (dd, 1H), 7.01 (s, 1H), 6.99 (m, 1H), 6.9 (dd, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 3.78 (s, 3H).

Example 87

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

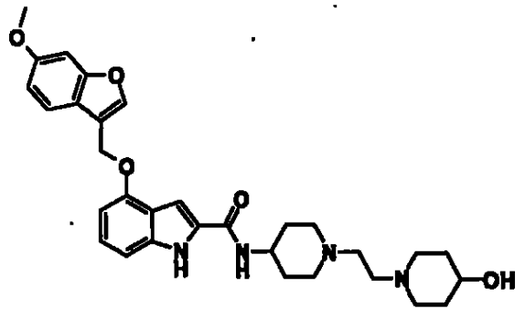


This compound is synthesized from 4-(6-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (120, see example 86) and amine 5 analogously to the method described in example 1.
Yield: 121 mg (50%). MS (ESI): 545 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.12 (d, 1H), 8.05 (s, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.91 (dd, 1H), 6.7

(d, 1H), 5.3 (s, 2H), 3.8 (s, 3H), 3.7 (m, 1H), 2.85 (m, 2H), 2.5 – 2.6 (m, 8H), 2.35 (dd, 2H), 2.0 (m, 2H), 1.72 (m, 2H), 1.45 – 1.6 (m, 8H).

Example 88

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

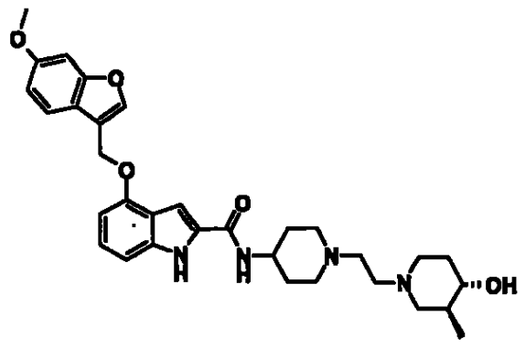


This compound is synthesized from 4-(6-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (120, see example 86) and amine 21 analogously to the method described in example 1.

Yield: 65 mg (27%). MS (ESI): 547 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.1 (br d, 1H), 8.03 (s, 1H), 7.55 (d, 1H), 7.18 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.9 (dd, 1H), 6.68 (d, 1H), 5.3 (s, 2H), 4.5 (br, 1H), 3.78 (s, 3H), 3.72 (m, 1H), 3.4 (m, 1H), 2.9 (m, 2H), 2.7 (m, 2H), 2.4 (m, 4H), 2.0 (m, 4H), 1.7 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Example 89

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

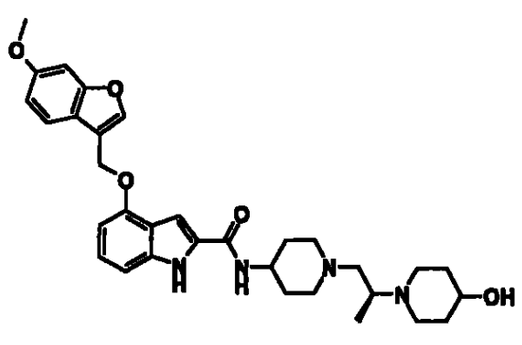


This compound is synthesized from 4-(6-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (120, see example 86) and amine 14 analogously to the method described in example 1.

Yield: 186 mg (89%). MS (ESI): 561 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 8.04 (s, 1H), 7.55 (d, 1H), 7.1 – 7.3 (m, 3H), 7.0 (d, 1H), 6.9 (dd, 1H), 6.71 (d, 1H), 5.34 (s, 2H), 2.6 – 4.2 (m, 14H), 1.75 – 2.2 (m, 8H), 0.93 (d, 3H).

Example 90

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

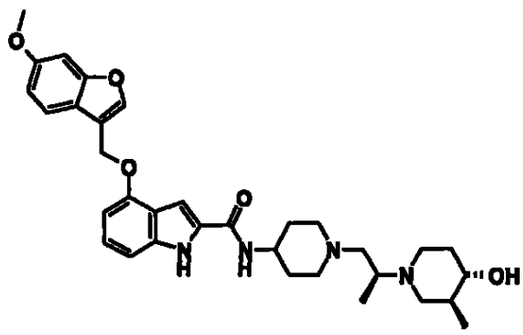


This compound is synthesized from 4-(6-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (120, see example 86) and amine 50 analogously to the method described in example 1.

Yield: 63 mg (38%). MS (ESI): 561 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.18 (d, 1H), 8.04 (s, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.9 (dd, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.75 (br, 1H), 2.6 – 4.1 (m, 7H), 0.9 – 2.4 (m, 20H).

Example 91

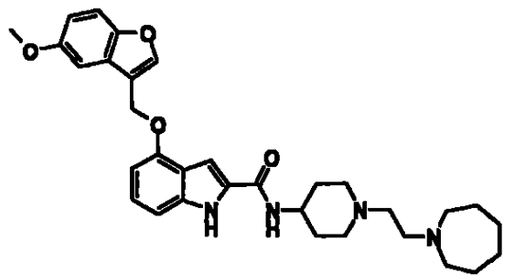
4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(6-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 120 (see example 86) and amine 56.
MS (ESI): 575.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.03 (s, 1H), 7.56 (d, 1H), 7.21 (d, 1H), 7.19 (s, 1H), 7.08 (t, 1H), 7.01 (d, 1H), 6.92 (d, 1H), 6.69 (d, 1H), 5.3 (s, 2H), 3.8 (s, 3H), 3.65-3.8 (m, 1H), 3.31 (m, 2H), 2.59-2.92 (m, 6H), 2.01-2.4 (m, 4H), 1.89 (m, 2H), 1.65-1.78 (m, 3H), 1.19-1.59 (m, 4H), 0.89 (d, 3H), 0.86 (d, 3H).

Example 92

4-(5-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



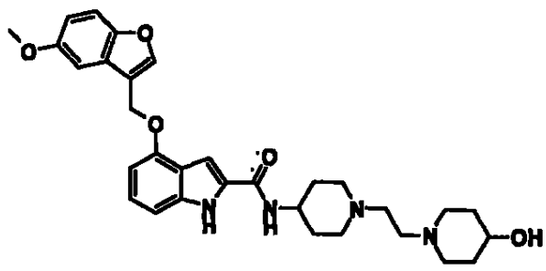
This compound is synthesized from 4-(5-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (121) (preparation see below) and amine 5 analogously to the method described in example 1.
Yield: 77 mg (48%). MS (ESI): 545 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.13 (m, 2H), 7.48 (d, 1H), 7.23 (s, 1H), 7.2 (d, 1H), 7.08 (dd, 1H), 7.02 (d, 1H), 6.92 (dd, 1H), 6.71 (d, 1H), 5.32 (s, 2H), 3.74 (s, 3H), 3.68 (m, 1H), 2.83 (m, 2H), 2.5 – 2.6 (m, 8H), 2.35 (dd, 2H), 1.98 (dd, 2H), 1.70 (m, 2H), 1.45 – 1.6 (m, 8H).

Synthesis of 4-(5-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (121):

This compound is synthesized from 4-methoxy-phenol analogously to the method described for 108 (see example 55).
460 mg (86%). MS (ESI): 336 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.73 (s, 1H), 8.1 (s, 1H), 7.46 (d, 1H), 7.22 (d, 1H), 7.15 (dd, 1H), 7.06 (d, 1H), 7.02 (d, 1H), 6.91 (dd, 1H), 6.73 (d, 1H), 5.37 (s, 2H), 3.75 (s, 3H).

Example 93

4-(5-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

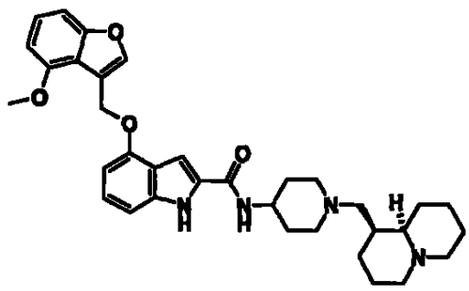


This compound is synthesized from 4-(5-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (121, see example 92) and amine 21 analogously to the method described in example 1.

Yield: 105 mg (65%). MS (ESI): 547 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.15 (d, 1H), 8.11 (s, 1H), 7.49 (d, 1H), 7.24 (s, 1H), 7.20 (d, 1H), 7.09 (dd, 1H), 7.02 (d, 1H), 6.93 (dd, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 4.51 (br, 1H), 3.75 (s, 3H), 3.7 (m, 1H), 3.41 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.39 (m, 4H), 2.0 (m, 4H), 1.71 (m, 4H), 1.52 (m, 2H), 1.35 (m, 2H).

Example 94

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (122) (preparation see below) and 1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-ylamine, 81.

MS (ESI): 571.2 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.75 (s, 1H), 7.27 (s, 1H), 7.25 (t, 1H), 7.18 (t, 1H), 7.10 (d, 1H), 7.07 (d, 1H), 6.75 (d, 1H), 6.67 (d, 1H), 5.43 (s, 2H), 4.15 (br s, 1H), 3.4-3.8 (br m, 7H), 3.83 (s, 3H), 2.8-3.25 (m, 4H), 2.53 (br m, 1H), 1.5-2.3 (m, 14H).

X36
135

Synthesis of 4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (122)

(1) 4-Methoxy-benzofuran-3-carbaldehyde, 123

To a solution of 4-methoxy-3-methyl-benzofuran (J. Chem. Res. Synopses (1996),132) (4 g, 24.66 mmol) in 40 ml of dioxane is added selenium dioxide (3.39 g, 29.59 mmol) and the mixture is heated under reflux for 24 hours. It is then cooled and filtered. The solvent is evaporated and the crude red solid is used as such in the next step.
Yield: 4.86 g (>100%). MS (ESI): 177.0 $[M+H]^+$.

(2) (4-Methoxy-benzofuran-3-yl)-methanol, 124

The aldehyde 123 from above (4.34 g, 24.63 mmol) is dissolved in 10 ml of methanol and cooled in an ice-bath. Solid sodium borohydride (4.9 g, 123.2 mmol) is added in portions and the mixture is stirred for 2 hours. It is then poured onto ice-cold HCl, extracted three times with DCM, dried and evaporated. The crude material is purified by chromatography on silicagel using hexane and EtOAc (from 20% to 50%).
Yield: 1.82 g (41%). MS (ESI): 196.1 $[M+NH_4]^+$.

(3) 4-(4-Methoxy-benzofuran-3-ylmethoxy)-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester, 125

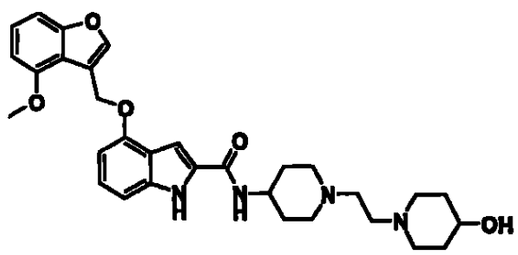
Indole ester 125 is prepared from alcohol 124 and 102 under Mitsunobu conditions (as described in example 50 for 105).
MS (ESI): 410.2 $[(M-CMe_3)+H]^+$.

(4) 4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 122

The title compound is prepared from ester 125 by cleavage with KOH/EtOH/THF (as described in example 50 for 105).
MS (ESI): 338.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.76 (s, 1H), 8.07 (s, 1H), 7.29 (t, 1H), 7.21 (s, 1H), 7.19 (t, 1H), 7.1 (s, 1H), 7.04 (d, 1H), 6.83 (d, 1H), 6.69 (d, 1H), 5.39 (s, 2H), 3.84 (s, 3H).

Example 95

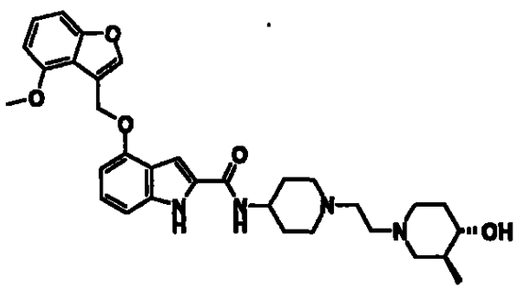
4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid 122 (see example 94) and amine 21.
MS (ESI): 547.2 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.63 (s, 1H), 7.13 (s, 1H), 7.12 (t, 1H), 7.04 (t, 1H), 6.98 (d, 1H), 6.94 (d, 1H), 6.62 (d, 1H), 6.53 (d, 1H), 5.3 (s, 2H), 3.76 (m, 1H), 3.71 (s, 3H), 3.54 (m, 1H), 2.85 (m, 2H), 2.73 (m, 2H), 2.42 (m, 4H), 2.07 (m, 4H), 1.81 (m, 2H), 1.74 (m, 2H), 1.53 (m, 2H), 1.45 (m, 2H).

Example 96

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

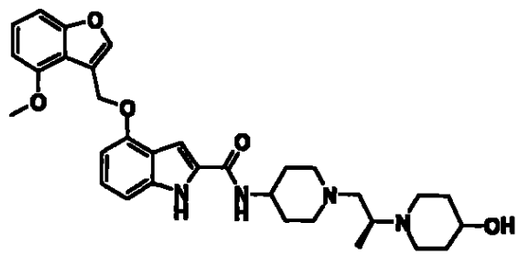


This compound is synthesized analogously to example 1 from 4-(4-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid 122 (see example 94) and amine 14.
MS (ESI): 561.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.09 (d, 1H), 8.01 (s, 1H), 7.27 (t, 1H), 7.23 (s, 1H), 7.2 (t, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.81 (d, 1H), 6.65 (d,

1H), 5.34 (s, 2H), 4.47 (d, 1H), 3.79 (s, 3H), 3.7 (m, 1H), 2.64-2.93 (m, 4H), 2.35 (m, 4H), 1.82-2.05 (m, 3H), 1.63-1.8 (m, 3H), 1.26-1.63 (m, 6H), 0.85 (d, 3H).

Example 97

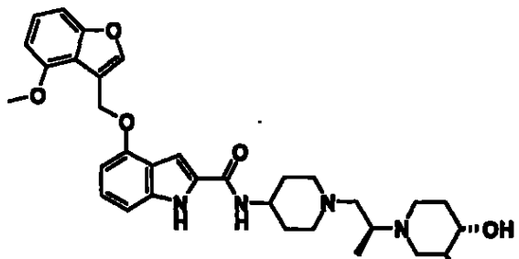
4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 122 (see example 84) and amine 50.
MS (ESI): 561.2 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.62 (s, 1H), 7.13 (s, 1H), 7.12 (t, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.94 (d, 1H), 6.62 (d, 1H), 6.52 (d, 1H), 5.3 (s, 2H), 3.74 (m, 1H), 3.71 (s, 3H), 3.46 (br m, 1H), 2.93 (m, 1H), 2.77 (m, 1H), 2.65-2.75 (m, 3H), 2.4 (m, 1H), 2.28 (m, 2H), 2.12 (m, 2H), 1.97 (m, 1H) 1.75 (m, 4H), 1.35-1.65 (m, 5H), 0.93 (d, 3H).

Example 98

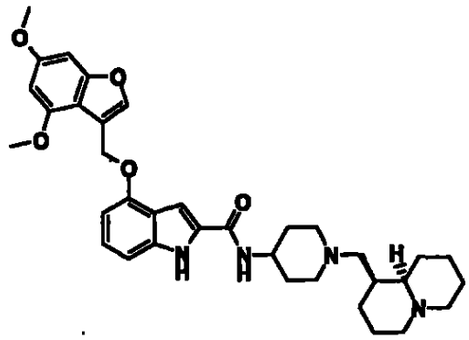
4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4-methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 122 (see example 94) and amine 56.
MS (ESI): 575.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.08 (m, 1H), 8.0 (s, 1H), 7.27 (t, 1H), 7.22 (s, 1H), 7.2 (t, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.81 (d, 1H), 6.65 (d, 1H), 5.34 (s, 2H), 4.42 (m, 1H), 3.79 (s, 3H), 3.73 (m, 1H), 2.58-2.92 (m, 6H), 2.31 (m, 1H), 2.22 (m, 1H), 2.02-2.17 (m, 2H), 1.89 (m, 2H), 1.66-1.78 (m, 3H), 1.2-1.6 (m, 4H), 0.9 (d, 3H), 0.86 (d, 3H).

Example 99

4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



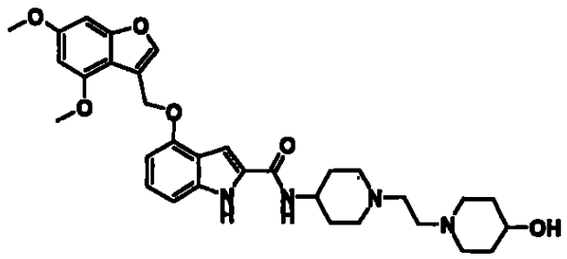
This compound is synthesized from 4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid 126 (preparation see below) and amine 61 analogously to the method described in example 1.
Yield: 146 mg (76.3%). MS (ESI): 601 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.1 – 10.7 (br, 2H), 8.1 – 8.5 (br, 1H), 7.89 (s, 1H), 7.3 (br s, 1H), 7.1 (dd, 1H), 7.0 (d, 1H), 6.8 (s, 1H), 6.62 (d, 1H), 6.42 (s, 1H), 5.28 (s, 2H), 4.0 (m, 1H), 3.8 (s, 3H), 3.75 (s, 3H), 2.8 – 3.8 (m, 14H), 1.3 – 2.1 (m, 12H).

Synthesis of 4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (126):

This compound is synthesized from 3,5-dimethoxyphenol analogously to the method described for 106 (see example 55).
MS (ESI): 366 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.78 (br s, 1H), 11.7 (s, 1H), 7.69 (s, 1H), 7.14 (dd, 1H), 7.08 (d, 1H), 7.02 (d, 1H), 6.78 (d, 1H), 6.65 (d, 1H), 6.41 (d, 1H), 5.31 (s, 2H), 3.79 (s, 3H), 3.31 (s, 3H).

Example 100

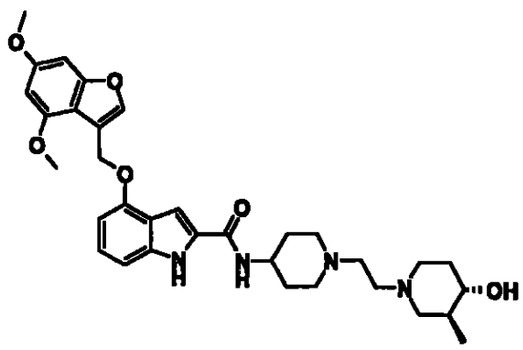
4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 126 (see example 99) and amine 21.
MS (ESI): 577.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.1 (d, 1H), 7.87 (s, 1H), 7.22 (s, 1H), 7.08 (t, 1H), 7.0 (d, 1H), 6.81 (s, 1H), 6.63 (d, 1H), 6.42 (s, 1H), 5.28 (s, 2H), 4.49 (m, 1H), 3.8 (s, 3H), 3.76 (s, 3H), 3.73 (m, 1H), 3.16 (m, 1H), 2.85 (m, 2H), 2.69 (m, 2H), 2.36 (m, 4H) 1.99 (m, 4H), 1.7 (m, 4H), 1.5 (m, 2H), 1.34 (m, 2H).

Example 101

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

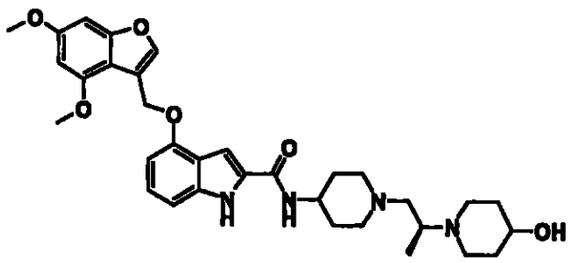


This compound is synthesized from 4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (126, see example 99) and amine 14 analogously to the method described in example 1.

Yield: 85 mg (47%). MS (ESI): 591 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 7.87 (s, 1H), 7.25 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.8 (d, 1H), 6.64 (d, 1H), 6.4 (d, 1H), 5.26 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 3.8 (s, 3H), 3.77 (s, 3H), 2.6 – 3.8 (m, 12H), 1.75 – 2.2 (m, 8H), 0.93 (d, 3H).

Example 102

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

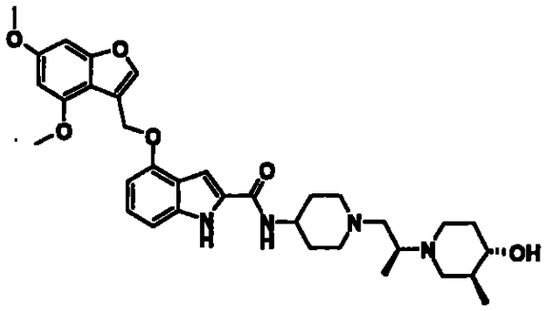


This compound is synthesized analogously to example 1 from 4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 126 (see example 99) and amine 50.

MS (ESI): 591.3 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.63 (s, 1H), 7.23 (s, 1H), 7.14 (t, 1H), 7.04 (d, 1H), 6.87 (s, 1H), 6.62 (d, 1H), 6.37 (s, 1H), 5.35 (d, 2H), 3.85 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.57 (m, 1H), 3.05 (m, 1H), 2.89 (m, 1H), 2.75-2.87 (m, 3H), 2.35-2.55 (m, 3H), 2.24 (m, 2H), 2.08 (m, 1H), 1.8-1.95 (m, 4H), 1.45-1.75 (m, 4H), 1.04 (d, 3H).

Example 103

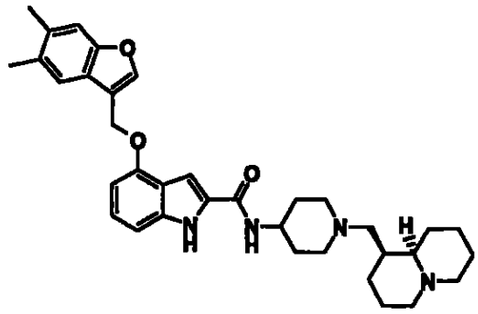
4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid, 126 (see example 99) and amine 56.
MS (ESI): 605.1 $[M+H]^+$, 1H-NMR (CD_3OD): δ (ppm) 7.64 (s, 1H), 7.23 (s, 1H), 7.15 (t, 1H), 7.05 (d, 1H), 6.69 (s, 1H), 6.64 (d, 1H), 6.38 (s, 1H), 4.85 (s, 2H), 3.88 (m, 1H), 3.84 (s, 3H), 3.8 (s, 3H), 2.78-3.17 (m, 6H), 2.57 (m, 1H), 2.23-2.47 (m, 3H), 2.03-2.21 (m, 2H), 1.87-1.98 (m, 3H), 1.45-1.8 (m, 4H), 1.08 (d, 3H), 0.99 (d, 3H).

Example 104

4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride



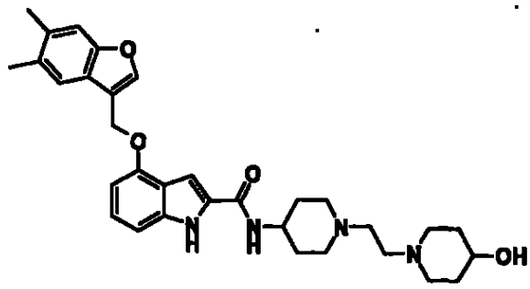
This compound is synthesized from 4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid 127 (preparation see below) and amine 61 analogously to the method described in example 1.
Yield: 146 mg (76.3%). MS (ESI): 569 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 10.4 – 10.4 (br, 2H), 8.5 (br, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 7.27 (br s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.0 (m, 1H), 2.8 – 3.8 (m, 14H), 2.32 (s, 3H), 2.28 (s, 3H), 1.3 – 2.1 (m, 12H).

Synthesis of 4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (127):

This compound is synthesized from 3,4-dimethylphenol analogously to the method described for 106 (see example 55).
MS (ESI): 334 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.9 (br s, 1H), 11.55 (s, 1H), 8.02 (s, 1H), 7.47 (s, 1H), 7.38 (s, 1H), 7.15 (dd, 1H), 7.0 (m, 2H), 6.7 (d, 1H), 5.3 (s, 2H), 2.35 (s, 3H), 2.3 (s, 3H).

Example 105

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

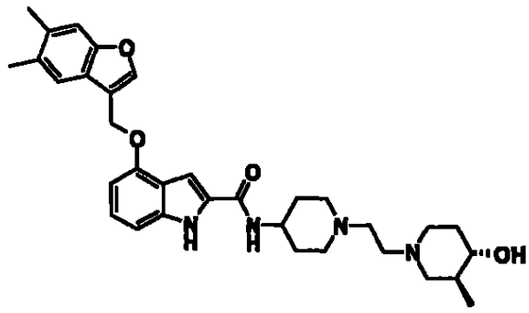


This compound is synthesized from 4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (127, see example 104) and amine 21 analogously to the method described in example 1.

Yield: 96 mg (51%). MS (ESI): 545.5 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.09 (d, 1H), 8.05 (s, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 7.10 (dd, 1H), 7.0 (d, 1H), 6.88 (s, 1H), 6.7 (d, 1H), 5.28 (s, 2H), 4.45 (d, 1H), 3.7 (m, 1H), 3.38 (m, 1H), 2.84 (m, 2H), 2.7 (m, 2H), 2.5 (s, 3H), 2.38 (s, 3H), 2.35 (m, 4H), 1.95 (m, 4H), 1.7 (m, 4H), 1.45 (m, 2H), 1.3 (m, 2H).

Example 106

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

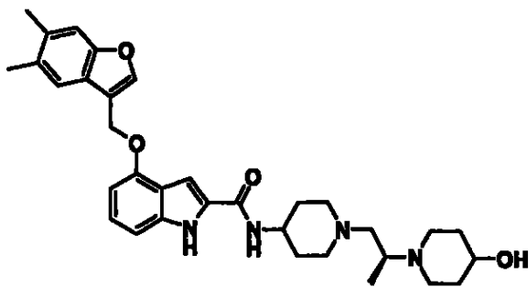


This compound is synthesized from 4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (127, see example 104) and amine 14 analogously to the method described in example 1.

Yield: 105 mg (56%). MS (ESI): 559 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 7.4 (s, 1H), 7.25 (d, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.29 (s, 2H), 4.05 (m, 1H), 2.6 – 3.8 (m, 13H), 2.33 (s, 3H), 2.3 (s, 3H), 1.75 – 2.2 (m, 8H), 0.93 (d, 3H).

Example 107

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

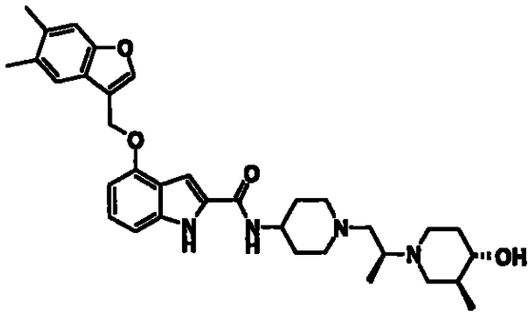


This compound is synthesized from 4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (127, see example 104) and amine 50 analogously to the method described in example 1.

Yield: 112 mg (56.6%). MS (ESI): 559 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.3 – 10.6 (br, 2H), 8.5 (d, 1H), 8.12 (s, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 7.25 (s, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 2.9 – 4.1 (m, 13H), 2.35 (s, 3H), 2.28 (s, 3H), 1.7 – 2.2 (m, 8H), 1.35 / 1.3 (d, 3H) (rotamers).

Example 108

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride



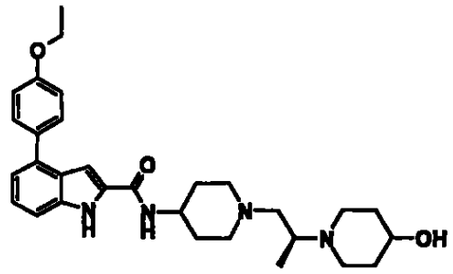
This compound is synthesized from 4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (127, see example 104) and amine 56 analogously to the method described in example 1.

Yield: 130 mg (68%). MS (ESI): 573 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4 - 10.6 (br, 2H), 8.52 (d, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 7.4 (s, 1H), 7.25 (s, 1H), 7.12 (dd,

1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 2.8 – 3.9 (m, 13H), 2.32 (s, 3H), 2.29 (s, 3H), 1.9 – 2.1 (m, 6H), 1.32 (d, 3H), 0.93 (d, 3H).

Example 109

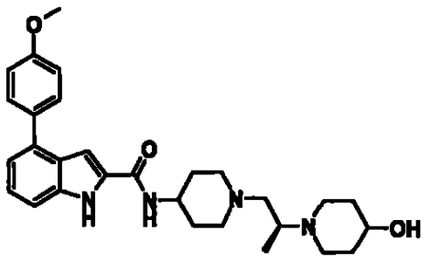
4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4-ethoxy-phenyl)-1H-indole-2-carboxylic acid, (preparation analogously to 128, see example 141) and amine 60. MS (ESI): 505.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.56 (d, 2H), 7.36 (d, 1H), 7.31 (s, 1H), 7.2 (t, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.48 (m, 1H), 4.09 (q, 2H), 3.76 (m, 1H), 3.37 (m, 1H), 2.58-2.96 (m, 5H), 1.85-2.43 (m, 6H), 1.42-1.83 (m, 6H), 1.37 (t, 3H), 1.33 (m, 2), 0.93 (d, 3H).

Example 110

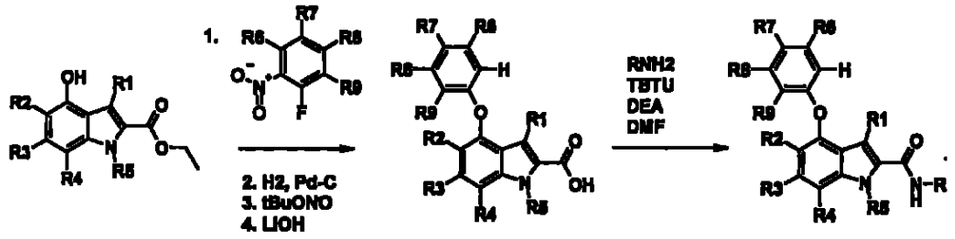
4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 1 from 4-(4-methoxy-phenyl)-1H-indole-2-carboxylic acid, 128 (see example 141) and amine 50.
MS (ESI): 491 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.59 (s, 1H), 8.23 (d, 1H), 7.58 (d, 2H), 7.34 (d, 1H), 7.31 (s, 1H), 7.2 (t, 1H), 7.06 (d, 2H), 7.01 (d, 1H), 4.44 (d, 1H), 3.81 (s, 3H), 3.75 (m, 1H), 2.96 (m, 1H), 2.6-2.95 (m, 5H), 2.04-2.4 (m, 5H), 1.92 (m, 1H), 1.2-1.85 (m, 8H), 0.91 (d, 3H).

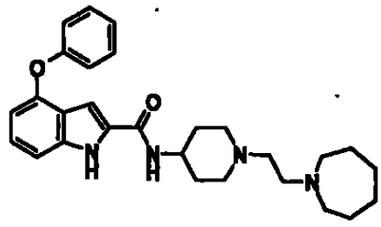
The 4-aryloxy-indole-2-carboxamides are generally prepared by a coupling of the 4-hydroxy-indole-2-carboxamides with the corresponding 1-fluoro-2-nitro-benzenes (Reaction Scheme 15).

Reaction Scheme 15:



Example 111

4-Phenoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-phenoxy-1H-indole-2-carboxylic acid 129 (preparation see below) and amine 5.
Yield: 105 mg (41%) of a beige solid; MS (ESI): 459.4 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.22 (d, 1H), 7.34 (dd, 2H), 7.24 (d, 1H), 7.04-7.15 (m, 3H), 6.95 (d, 2H), 6.55

(d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.52 – 2.6 (m, 6H), 2.38 (m, 2H), 2.0 (t, 4H), 1.72 (m, 2H), 1.48 (m, 8H).

Synthesis of 4-Phenoxy-1H-indole-2-carboxylic acid (129):

(1) Step A: 4-(2-Nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (130)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (0.5 g, 2.436 mmol) and 2-fluoro-nitrobenzene (0.257 ml, 2.436 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (0.67 g, 4.87 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
Yield: 0.72 g (91%) of a beige solid. MS (ESI): 325.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 8.1 (d, 1H), 7.6 (dd, 1H), 7.32 (m, 2H), 7.25 (dd, 1H), 7.03 (d, 1H), 6.85 (m, 1H), 6.7 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(2) Step B: 4-(2-Amino-phenoxy)-1H-indole-2-carboxylic acid ethyl (131)

130 (0.5 g, 1.532 mmol) is dissolved in 100 ml of ethanol and, after addition of Pd-C (100 mg), the mixture is hydrogenated at room temperature for 3 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
Yield: 390 mg (86%) of a grey solid. MS (ESI): 297 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.95 (s, 1H), 7.13 (m, 2H), 7.0 (s, 1H), 6.88 (m, 1H), 6.8 (dd, 1H), 6.75 (dd, 1H), 6.5 (m, 1H), 6.38 (m, 1H), 4.9 (br, 2H), 4.3 (q, 2H), 1.3 (t, 3H).

(3) Step C: 4-Phenoxy-1H-indole-2-carboxylic acid ethyl ester (132)

Tert-butyl nitrite (0.2 ml, 1.687 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of 131 (0.5 g, 1.687 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (370 mg of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).

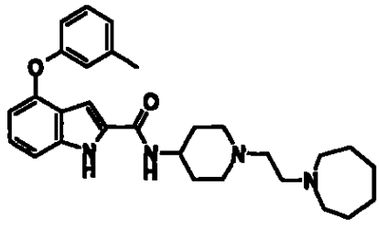
Yield: 163 mg (34%) of a yellow solid; MS (ESI): 280.2 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.05 (s, 1H), 7.37 (d, 1H), 7.35 (d, 1H), 7.23 (m, 2H), 7.1 (dd, 1H), 7.0 (d, 2H), 6.82 (s, 1H), 6.6 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: -Phenoxy-1H-Indole-2-carboxylic acid (129)

132 (160 mg, 0.569 mmol) is dissolved in 5 ml of methanol and treated with a solution of LiOH (27.2 mg, 1.138 mmol) in 3 ml of water. The mixture is stirred at room temperature overnight. Since the reaction is not complete (TLC), additional LiOH (30 mg, 1.25 mmol) is added and the stirring is continued for additional 18h. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
Yield: 146 mg (100%) of a yellow solid; MS (ESI): 253 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.9 (s, 1H), 7.38 (d, 1H), 7.34 (d, 1H), 7.2 (m, 2H), 7.12 (m, 1H), 7.0 (d, 2H), 6.75 (s, 1H), 6.58 (d, 1H).

Example 112

4-m-Tolyloxy-1H-Indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-m-tolyloxy-1H-Indole-2-carboxylic acid 133 (preparation see below) and amine 5.
Yield: 12 mg (11.3%) of a white solid; MS (ESI): 473.3 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.2 (d, 1H), 7.2 (m, 2H), 7.1 (m, 2H), 6.88 (d, 1H), 6.78 (m, 1H), 6.7 (m, 1H), 6.54 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.48 – 2.58 (m, 8H), 2.35 (m, 2H), 2.25 (s, 3H),1.98 (m, 2H), 1.75 (m, 2H), 1.48 – 1.55 (m, 8H).

Synthesis of 4-m-Tolyloxy-1H-indole-2-carboxylic acid (133):

(1) **Step A: 4-(5-Methyl-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (134)**

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 2-Fluoro-4-methyl-1-nitro-benzene (756 mg, 4.87 mmol) are dissolved in 20 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
Yield: 1.59 g (96%) of a beige solid. MS (ESI): 341 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 7.98 (d, 1H), 7.3 (d, 1H), 7.25 (dd, 1H), 7.15 (d, 1H), 6.88 (d, 1H), 6.63 (d, 1H), 4.3 (q, 2H), 2.28 (s, 3H),1.3 (t, 3H).

(2) **Step B: 4-(2-Amino-5-methyl-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (135)**

134 (1.3 g, 3.82 mmol) is dissolved in 250 ml of ethyl acetate and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 3 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
Yield: 1.12 g (95%) of a grey solid. MS (ESI): 311 $[M+H]^+$]+, 1H-NMR (DMSO-d_6): δ (ppm) 11.95 (br, 1H), 7.13 (m, 2H), 7.03 (s, 1H), 6.72 (s, 2H), 6.58 (s, 1H), 6.37 (m, 1H), 4.88 (br, 2H), 4.3 (q, 2H), 2.08 (s, 3H), 1.3 (t, 3H).

(3) **Step C: 4-m-Tolyloxy-1H-indole-2-carboxylic acid ethyl ester (136)**

Tert-butyl nitrite (0.428 ml, 3.609 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of 135 (1.1 g, 3.609 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (930 mg of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 7:3).

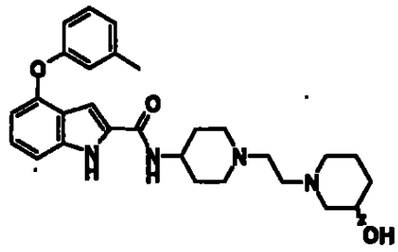
Yield: 520 mg (49%) of a yellow solid; MS (ESI): 294.2 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.0 (s, 1H), 7.18-7.24 (m, 3H), 6.92 (m, 1H), 6.82 (m, 2H), 6.78 (dd, 1H), 6.58 (dd, 1H), 4.28 (q, 2H), 2.27 (s, 3H),1.3 (t, 3H).

(4) Step D: 4-m-Tolyloxy-1H-indole-2-carboxylic acid (133)

136 (520 mg, 1.761 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (84.3 mg, 3.52 mmol) in 5 ml of water. The mixture is stirred at room temperature for 16 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
Yield: 460 mg (98%) of a beige solid; MS (ESI): 266.1 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.9 (s, 1H), 7.15-7.25 (m, 3H), 6.9 (m, 1H), 6.84 (m, 1H), 6.78 (m, 2H), 6.57 (m, 1H), 2.27 (s, 3H).

Example 113

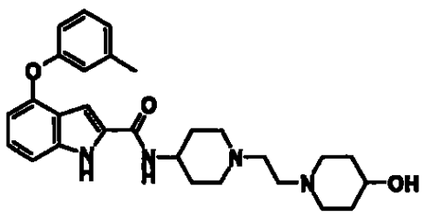
4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-m-Tolyloxy-1H-indole-2-carboxylic acid 133 (see example 112) and racemic amine 12.
Yield: 34 mg (21%) of a yellow solid; MS (ESI): 477.3 $[M+H]^+$, 1H-NMR (80°C, DMSO-d_6): δ (ppm) 11.2 (s, 1H), 7.77 (d, 1H), 7.24 (dd, 1H), 7.2 (dd, 1H), 7.1 (ss, 1H), 7.04 (s, 1H), 6.88 (d, 1H), 6.8 (m, 1H), 6.75 (m, 1H), 6.54 (d, 1H), 3.75 (m, 1H), 3.5 (m, 1H), 2.7-2.9 (m, 4H), 2.6 (m, 1H), 2.44 (m, 4H), 2.3 (s, 3H),2.13 (m, 2H), 2.05 (m, 1H), 1.95 (m, 1H), 1.7-1.85 (m, 3H), 1.55-1.65 (m, 3H), 1.4 (m, 1H), 1.15 (m, 1H).

Example 114

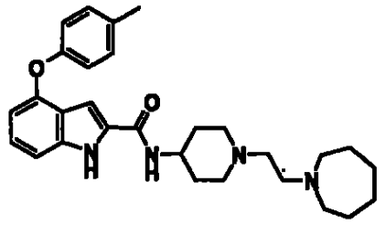
4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-m-tolyloxy-1H-indole-2-carboxylic acid 133 (see example 112) and amine 21.
Yield: 45 mg (28%) of a white solid; MS (ESI): 477 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.2 (m, 2H), 7.1 (m, 2H), 6.88 (d, 1H), 6.78 (m, 1H), 6.7 (m, 1H), 6.54 (d, 1H), 4.47 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.38 (m, 4H), 2.28 (s, 3H),1.98 (m, 4H), 1.63-1.75 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Example 115

4-p-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-p-tolyloxy-1H-indole-2-carboxylic acid 137 (preparation see below) and amine 6.
Yield: 12 mg (11.3%) of a white solid; MS (ESI): 473.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.18 (d, 1H), 7.05 – 7.2 (m, 5H), 6.85 (d, 2H), 6.47 (m, 1H), 3.7 (m, 1H), 2.85 (m, 2H), 2.47 – 2.58 (m, 6H), 2.35 (m, 2H), 2.25 (s, 3H),1.98 (m, 2H), 1.75 (m, 2H), 1.48 – 1.55 (m, 10H).

Synthesis of 4-p-Tolyloxy-1H-indole-2-carboxylic acid (137):

(1) Step A: 4-(3,5-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (138)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 1-Fluoro-4-methyl-2-nitro-benzene (0.6 ml, 4.87 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product (1.51 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).
Yield: 570 mg (34%) of a white solid. MS (ESI): 341 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.88 (d, 1H), 7.45 (dd, 1H), 7.27 (d, 1H), 7.22 (dd, 1H), 6.98 (d, 1H), 6.87 (s, 1H), 6.6 (d, 1H), 4.3 (q, 2H), 2.35 (s, 3H),1.3 (t, 3H).

(2) Step B: 4-(2-Amino-4-methyl-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (139)

138 (570 mg, 1.675 mmol) is dissolved in 150 ml of ethanol and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
Yield: 3.08g (100%) of a brown oil. MS (ESI): 311 $[M+H]^+$.

(3) Step C: 4-p-Tolyloxy-1H-indole-2-carboxylic acid ethyl ester (140)

Tert-butyl nitrite (0.176 ml, 1.48 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of 139 (460 mg, 1.48 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (420 mg of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).

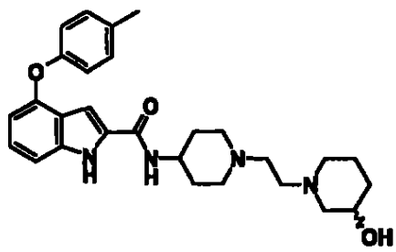
Yield: 70 mg (16%) of a yellow solid; MS (ESI): 294.2 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.0 (s, 1H), 7.15-7.24 (m, 4H), 7.4 (m, 2H), 6.85 (d, 1H), 6.52 (dd, 1H), 4.3 (q, 2H), 2.28 (s, 3H),1.3 (t, 3H).

(4) Step D: 4-p-Tolyloxy-1H-indole-2-carboxylic acid (137)

140 (70 mg, 0.237 mmol) is dissolved in 5 ml of methanol and treated with a solution of LiOH (11.4 mg, 0.474 mmol) in 3 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
Yield: 60 mg (100%) of a beige solid; MS (ESI): 266.2 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.8 (s, 1H), 7.13-7.2 (m, 4H), 6.9 (m, 2H), 6.77 (d, 1H), 6.52 (dd, 1H), 2.29 (s, 3H).

Example 116

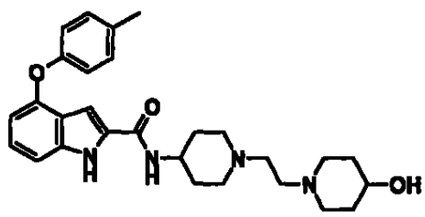
4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-p-tolyloxy-1H-indole-2-carboxylic acid 137 (see example 115) and racemic amine 12.
Yield: 87 mg (49%) of a beige solid; MS (ESI): 475.3 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8. 2 (d, 1H), 7.08-7.2 (m, 5H), 6.87 (d, 2H), 6.47 (d, 1H), 4.53 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 3H), 2.65 (m, 1H), 2.37 (m, 4H), 2.28 (s, 3H), 1.98 (t, 2H), 1.7-1.85 (m, 5H), 1.55 (m, 3H), 1.35 (m, 1H), 1.05 (m, 1H).

Example 117

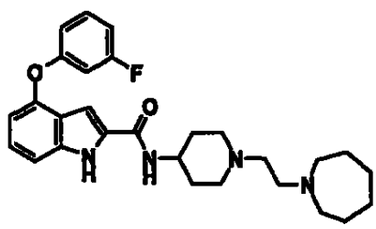
4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-p-tolyloxy-1H-indole-2-carboxylic acid 137 (see example 116) and amine 21.
Yield: 80 mg (45%) of a beige solid; MS (ESI): 475.3 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8. 2 (d, 1H), 7.07-7.2 (m, 5H), 6.85 (d, 2H), 6.47 (d, 1H), 4.48 (br, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.35 (m, 4H), 2.27 (s, 3H), 1.95-2.05 (m, 4H), 1.65-1.75 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Example 118

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid 141 (preparation see below) and amine 5.
Yield: 50 mg (28.3%) of a white solid; MS (ESI): 479.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.2 (d, 1H), 7.35 (dd, 1H), 7.28 (d, 1H), 7.18 (dd, 1H), 7.05 (s, 1H), 6.9 (dd, 1H), 6.73-6.8 (m, 2H), 6.66 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.5–2.58 (m, 6H), 2.35 (m, 2H), 1.98 (m, 2H), 1.72 (m, 2H), 1.48 – 1.55 (m, 10H).

Synthesis of 4-p-Tolyloxy-1H-indole-2-carboxylic acid (141):

(1) **Step A: 4-(3,5-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (142)**

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 2,4-Difluoro-1-nitro-benzene (0.534 ml, 4.87 mmol) are dissolved in 20 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
Yield: 1.63 g (97%) of a grey resin; MS (ESI): 343.1 $[M-H]^-$.

(2) **Step B: 4 4-(2-Amino-5-fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (143)**

142 (1.6 g, 4.734 mmol) is dissolved in 250 ml of ethyl acetate and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
Yield: 1.41 g (95%) of a grey foam. MS (ESI): 315.2 $[M+H]^+$.

(3) **Step C: 4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (144)**

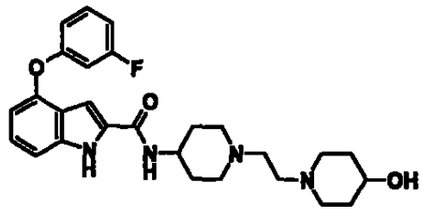
Tert-butyl nitrite (0.46 ml, 4.45 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of 143 (1.4 g, 4.45 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.0 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 7:3).
Yield: 440 mg (33%) of a yellow solid; MS (ESI): 298.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.35 (dd, 1H), 7.3 (d, 1H), 7.25 (dd, 1H), 6.92 (dd, 1H), 6.77-6.87 (m, 3H), 6.7 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: 4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid (141)

144 (440 mg, 1.47 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (70 mg, 1.47 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
Yield: 420 mg (100%) of a yellow solid; MS (ESI): 270.1 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.95 (s, 1H), 11.9 (s, 1H), 7.35 (dd, 1H), 7.28 (d, 1H), 7.18 (dd, 1H), 6.9 (dd, 1H), 6.77-6.65 (m, 2H), 6.75 (s, 1H), 6.7 (d, 1H).

Example 119

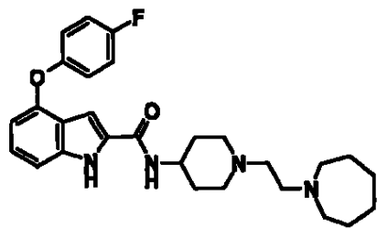
4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-(3-fluoro-phenoxy)-1H-indole-2-carboxylic acid 141 (see example 118) and amine 21.
Yield: 35 mg (20%) of a white solid; MS (ESI): 479 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.21 (d, 1H), 7.35 (dd, 1H), 7.29 (d, 1H), 7.18 (dd, 1H), 7.05 (s, 1H), 6.9 (dd, 1H), 6.73-6.6 (m, 2H), 6.68 (d, 1H), 4.49 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.37 (m, 4H), 1.95 (m, 4H), 1.83-1.77 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Example 120

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(4-fluoro-phenoxy)-1H-indole-2-carboxylic acid 145 (preparation see below) and amine 5.
Yield: 86 mg (49%) of a white solid; MS (ESI): 477.3 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.2 (d, 1H), 7.14-7.24 (m, 5H), 7.0 (m, 2H), 6.5 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.5–2.6 (m, 6H), 2.36 (m, 2H), 1.98 (m, 2H), 1.72 (m, 2H), 1.48 – 1.57 (m, 10H).

Synthesis of 4-p-Tolyloxy-1H-indole-2-carboxylic acid (145):

(1) **Step A: 4-(4-Fluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (146)**

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (0.92 g, 4.483 mmol) and 1,4-Difluoro-2-nitro-benzene (0.486 ml, 4.483 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.2 g, 8.96 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
Yield: 1.45 g (94%) of a grey resin; MS (ESI): 343.1 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 8.08 (m, 1H), 7.55 (m, 1H), 7.3 (d, 1H), 7.24 (dd, 1H), 7.15 (dd, 1H), 6.9 (s, 1H), 6.82 (d, 1H), 4.3 (q, 2H), 1.32 (t, 3H).

(2) **Step B: 4-(2-Amino-4-fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (147)**

146 (1.5 g, 4.21 mmol) is dissolved in 200 ml of ethyl acetate and, after addition of Pd-C (200 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.

Yield: 1.31 g (99%) of a beige solid. MS (ESI): 313.2 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.95 (s, 1H), 7.12 (m, 2H), 7.05 (m, 1H), 6.75 (dd, 1H), 6.58 (dd, 1H), 6.34 (m, 1H), 6.28 (dt, 1H), 5.25 (br, 2H), 4.3 (q, 2H), 1.32 (t, 3H).

(3) Step C: 4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (148)

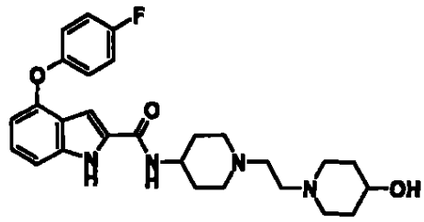
Tert-butyl nitrite (0.46 ml, 4.45 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of 147 (1.4 g, 4.45 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.0 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 7:3).
Yield: 440 mg (33%) of a yellow solid; MS (ESI): 298.2 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.05 (s, 1H), 7.2 (m, 4H), 7.05 (m, 2H), 6.85 (m, 1H), 6.54 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: 4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid (145)

148 (510 mg, 1.7 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (82 mg, 3.4 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
Yield: 460 mg (100%) of a yellow solid; MS (ESI): 270.1 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 13.0 (s, 1H), 11.9 (s, 1H), 7.15-7.22 (m, 4H), 7.05 (m, 2H), 6.78 (m, 1H), 6.55 (d, 1H).

Example 121

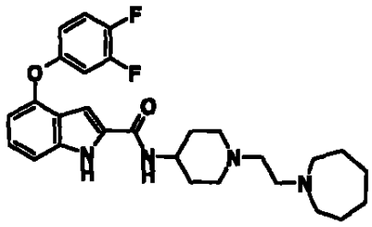
4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-(4-fluoro-phenoxy)-1H-indole-2-carboxylic acid 145 (see example 120) and amine 21.
Yield: 68 mg (37%) of a white solid; MS (ESI): 479 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.1-7.24 (m, 5H), 7.0 (m, 2H), 6.5 (d, 1H), 4.46 (br, 1H), 3.72 (m, 1H), 3.42 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.64-1.77 (m, 4H), 1.53 (m, 2H), 1.35 (m, 2H).

Example 122

4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid 149 (preparation see below) and amine 5.
Yield: 62 mg (36%) of a white solid; MS (ESI): 495.3 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.23 (d, 1H), 7.44 (m, 1H), 7.26 (d, 1H), 7.14 (m, 1H), 7.0 (m, 1H), 6.80 (m, 1H), 6.56 (d, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.5-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47 – 1.55 (m, 10H).

Synthesis of 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid (149):

(1) **Step A: 4-(3,5-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (150)**

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 1,2,4-Trifluoro-5-nitro-benzene (0.559 ml, 4.87 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved

with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated.
Yield: 1.79g (100%) of a yellow foam. MS (ESI): 361.1 [M-H]⁻.

(2) Step B: 4-(2-Amino-4,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (151)

150 (1.8 g, 4.87mmol) is dissolved in 150 ml of ethyl acetate and, after addition of Pd-C (500 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
Yield: 1.61g (99%) of a brown foam. MS (ESI): 333.2 $[M+H]^+$.

(3) Step C: 4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (152)

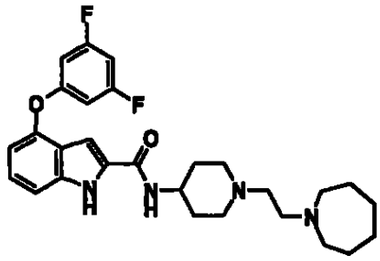
Tert-butyl nitrite (0.575 ml, 4.85 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of 151 (1.6g, 4.85 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.78 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).
Yield: 380 mg (25%) of a slightly yellow solid; MS (ESI): 316.2 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.45 (m, 1H), 7.27 (d, 1H), 7.2 (dd, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 6.95 (m, 1H), 6.55 (d, 1H), 4.3 (q, 2H), 1.34 (t, 3H).

(4) Step D: 4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid (149)

152 (380 mg, 1.2 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (57 mg, 2.4 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
Yield: 310 mg (90%) of a yellow solid; MS (ESI): 288.1 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 13.0 (s, 1H), 12.0 (s, 1H), 7.45 (m, 1H), 7.25 (d, 1H), 7.18 (dd, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 6.87 (s, 1H), 6.55 (d, 1H).

Example 123

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(3,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid 153 (preparation see below) and amine 5.
Yield: 180 mg (33.2%) of a yellow solid; MS (ESI): 495.3 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.21 (d, 1H), 7.33 (d, 1H), 7.2 (dd, 1H), 7.04 (d, 1H), 6.94 (m, 1H), 6.75 (d, 1H), 6.62 (m, 2H), 3.7 (m, 1H), 2.85 (m, 2H), 2.47 – 2.58 (m, 6H), 2.36 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.47 – 1.55 (m, 10H).

Synthesis of 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid (153):

(1) Step A: 4-(3,5-Difluoro-2-nitro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (154)

4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (1 g, 4.87 mmol) and 1,3,5-Trifluoro-2-nitro-benzene (0.57 ml, 4.87 mmol) are dissolved in 10 ml of dimethylformamide. After addition of potassium carbonate (1.3 g, 9.74 mmol) the mixture is stirred over night at room temperature. Then the reaction mixture is evaporated under reduced pressure, dissolved with ethyl acetate and washed with water. The organic layers are dried over sodium sulfate and evaporated.
Yield: 1.8g (100%) of a yellow foam. MS (ESI): 361.2 [M-H]⁻.

(2) Step B: 4-(2-Amino-3,5-difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (155)

154 (1.8 g, 4.87mmol) is dissolved in 150 ml of ethyl acetate and, after addition of Pd-C (500 mg), the mixture is hydrogenated at room temperature for 2 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
Yield: 1.53g (94%) of a brown foam. MS (ESI): 333.2 $[M+H]^+$.

(3) Step C: 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid ethyl ester (156)

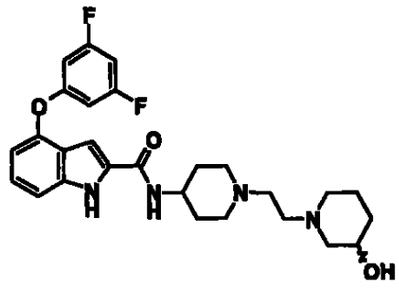
Tert-butyl nitrite (0.547 ml, 4.6 mmol) is dissolved in 5 ml of dimethylformamide and heated to 65°C. A solution of 155 (1.5g, 4.6 mmol) in 5 ml of dimethylformamide is added dropwise and the mixture is stirred of additional 10 minutes. The brown solution is cooled to room temperature, diluted with diethyl ether and washed with 2N HCl and brine. The organic layers are dried over sodium sulphate and evaporated. The crude product (1.5 g of a brown oil) is further purified by flash-chromatography (hexane / ethyl acetate 9:1).
Yield: 260 mg (17.8%) of a yellow solid; MS (ESI): 316.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 12.2 (s, 1H), 7.35 (d, 1H), 7.28 (dd, 1H), 6.95 (m, 1H), 6.82 (d, 1H), 6.79 (d, 1H), 6.66 (dd, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Step D: 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid (153)

156 (260 mg, 0.82 mmol) is dissolved in 10 ml of methanol and treated with a solution of LiOH (40 mg, 1.6 mmol) in 5 ml of water. The mixture is stirred at room temperature for 18 hours. After evaporation, the crude product is acidified at 0°C with 2M HCl and extracted with ethyl acetate. The organic layers are dried over sodium sulphate and evaporated.
Yield: 240 mg (100%) of a yellow solid;

Example 124

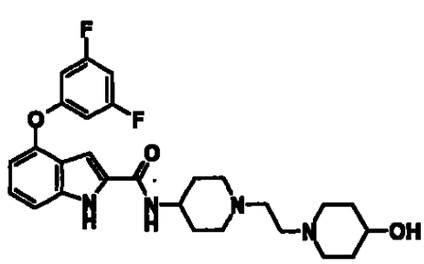
4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(3-RS-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid 153 (see example 123) and racemic amine 12.
Yield: 38 mg (32%) of a white solid; MS (ESI): 499 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.25 (d, 1H), 7.33 (d, 1H), 7.2 (dd, 1H), 7.04 (s, 1H), 6.92 (dd, 1H), 6.76 (d, 1H), 6.63 (d, 2H), 4.02 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.8-2.9 (m, 3H), 2.67 (m, 2H), 2.38 (m, 4H), 1.99 (m, 2H), 1.68-1.88 (m, 5H), 1.47-1.6 (m, 3H), 1.371 (m, 1H), 1.05 (m, 1H).

Example 125

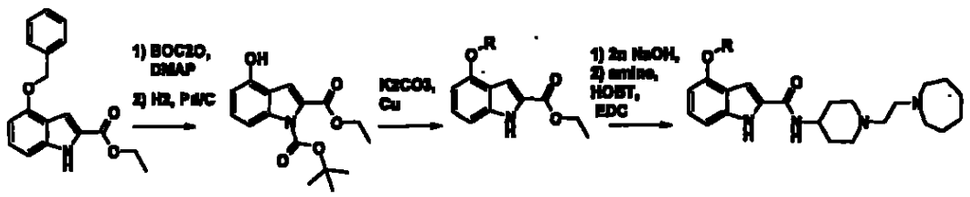
4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to Example 1 from 4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid 153 (see example 123) and amine 21.
Yield: 23 mg (13%) of a white solid; MS (ESI): 497.2 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.79 (s, 1H), 8.22 (br, 1H), 7.32 (d, 1H), 7.2 (dd, 1H), 7.04 (s, 1H), 6.9 (dd, 1H), 6.75 (d, 1H), 6.6 (d, 2H), 4.46 (s, 1H), 3.72 (m, 1H), 3.39 (m, 1H), 2.83 (m, 2H), 2.67 (m, 2H), 2.35 (m, 4H), 1.98 (m, 4H), 1.75 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.35 (m, 2H).

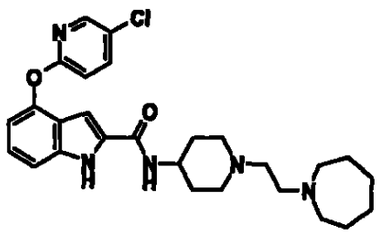
Alternatively, the 4-alkoxy-indole-2-carboxamides are prepared as shown in reaction scheme 16.

Reaction Scheme 1116:



Example 126

4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid 157 (preparation see below) and amine 5.
Yield: 85 mg (54%) of yellow crystals; MS (ESI): 494.3 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.2 (d, 1H), 7.85 (dd, 1H), 7.3 (d, 1H), 7.2 (m, 2H), 6.95 (s, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 3.7 (m, 1H), 2.85 (m, 2H), 2.5 – 2.6 (m, 6H), 2.35 (m, 2H), 2.0 (t, 2H), 1.75 (m, 2H), 1.5 (m, 10H).

Synthesis of 4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid (157):

(1) Step A: 4-Benzyloxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (158)

4-Benzyloxy-1H-indole-2-carboxylic acid ethyl ester (10 g, 34 mmol) and DMAP (80 mg) are dissolved in 80 ml of ethyl acetate. BOC2O (8.9 g, 41 mmol) dissolved in a small amount of ethyl acetate is added at room temperature. The mixture is stirred over night at room temperature. Then the reaction mixture is washed with 1m aqueous tartaric acid, water and brine. The organic layers are dried over sodium sulfate and evaporated. The crude product is used in the next step without further purification.
Yield: 13.6 g (100%) of a yellow oil. 1H-NMR (CDCl3): δ (ppm) 7.7 (d, 1H), 7.3 – 7.5 (m, 7H), 6.75 (d, 1H), 5.2 (s, 2H), 4.4 (q, 2H), 1.7 (s, 9H), 1.4 (t, 3H).

(2) **Step B: 4-Hydroxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (159)**

158 (8 g, 20 mmol) is dissolved in 80 ml of ethyl acetate and, after addition of 5% Pd-C (700 mg), the mixture is hydrogenated at room temperature for 7 hours. The mixture is filtrated over celite to remove the catalyst and evaporated. The solid is suspended in ether/hexane and filtered.
Yield: 4.6 g (74%). 1H-NMR (CDCl3): δ (ppm) 7.7 (d, 1H), 7.3 (m, 2H), 6.7 (d, 1H), 5.5 (s, 1H), 4.4 (q, 2H), 1.7 (s, 9H), 1.4 (t, 3H).

(3) **Step C: 4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid ethyl ester (160)**

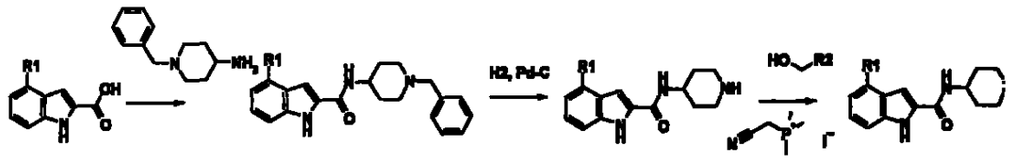
159 (500 mg, 1.6 mmol), 2,6-Dichloro-pyridine (360 mg, 24 mmol) are dissolved in 15 ml of dimethylformamide. After addition of potassium carbonate (340 mg, 24 mmol) and a catalytic amount Cu-powder the mixture is heated to 160°C for 3 hours. The reaction mixture is cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layers are dried over sodium sulphate and evaporated. The crude product is solved in dichloromethane and after evaporation crystallized with cyclohexane.
Yield: 300 mg (58%) of a beige solid. MS (ESI): 317.2 $[M+H]^+$, 1H-NMR (CDCl3): δ (ppm) 9.2 (br, 1H), 7.7 (dd, 1H), 7.3 (m, 2H), 7.1 (m, 2H), 6,95 (dd, 1H), 6.75 (d, 1H), 4.4 (q, 2H), 1.4 (t, 3H).

(4) **Step D: 4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid (157)**

160 (100 mg, 0.315 mmol) is dissolved in 4 ml of methanol and treated with a solution of NaOH (1 ml , 2N). The mixture is stirred 1 hour at room temperature. The reaction mixture is acidified with HCl (1 ml, 2N) and evaporated. The crude mixture is used in the next step without further purification.

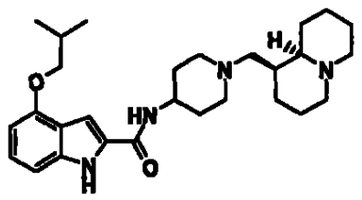
Alternatively, the 4-alkoxy-indole-2-carboxamides are prepared as shown in reaction scheme 17.

Reaction Scheme 17:



Example 127

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide dihydrochloride



161 (preparation see below) (2.5 g, 7.1 mmol), octahydro-2H-chinolizin-1-ylmethanol (Lupinine) (1.2 g, 7.1 mmol) and ethyldiisopropylamine (12.2 ml, 71 mmol) are dissolved in 10 ml of propionitril. After addition of cyanomethyl-trimethyl-phosphonium iodide (4.1 g, 17 mmol) the mixture is refluxed for 3h. After cooling down to room temperature, the mixture is diluted with ethyl acetate and washed with potassium carbonate solution. The crude product 3.9 g of a brown oil) is crystallized from methanol.

Yield: 2 g (52%) of a white solid. MS (ESI): 467 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.42 (s, NH), 8.16 (d, NH), 7.22(d, 1H), 7.02 (dd, 1H), 6.96(d, 1H) ,6,45(d, 1H), 3.83 (d, 2H), 3.75

(m,1H), 3.49(s,2H), 2.81(m, 2H), 2.70(m,2H), 2.29 (m, 1H), 2.15-2,00 (m, 2H),1,95-1,73 (m, 7H), 1.72-1.27 (m, 9H), 1.26-1,10(m, 2H), 1.05 (d, 6H).

Synthesis of 4-isobutoxy-1H-indole-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (161):

(1) Step A: 4-isobutoxy-1H-indole-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (161)

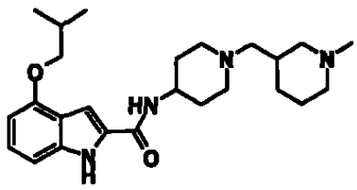
4-isobutoxy-1H-indole-2-carboxylic acid 80 (4.7g, 20.1 mmol, preparation see Example 8) and 1-benzyl-piperidin-4-ylamine (4.2 ml, 20.1 mmol) are dissolved in 70 ml of DMF and after addition of TBTU (7.3 g, 22.1 mmol) and ethyldiisopropylamine (13.8 ml, 80.4 mmol) the mixture is stirred at room temperature for 2 h. Then the solvent is evaporated at high vacuum. The residue is dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen arbonate and brine. The organic layers are dried over sodium sulfate and evaporated under reduced pressure.
Yield: 8.96 g of a beige solid. MS (ESI): 406.5 $[M+H]^+$

(2) Step B: 4-isobutoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide hydrochloride (161)

161 (8.1 g, 20 mmol) is dissolved in 200 ml of ethanol and, after addition of Pd-C (200 mg) and 10 ml of 4M HCl the mixture is hydrogenated at room temperature for 3 hours. The mixture is filtrated over celite to remove the catalyst and evaporated.
Yield: 7.13 g (100%) of a white solid. MS (ESI): 316 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.42 (d, 1H), 7.25 (s, 2H), 7.04 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 4.0 (m, 1H), 3.83 (d, 2H), 3.22 (m, 2H), 2.88 (m, 2H), 2.1 (m, 1H), 1.9 (m, 2H), 1.7 (m, 2H), 1.05 (d, 6H).

Example 128

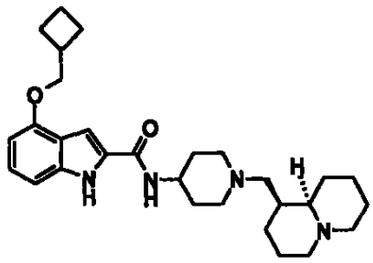
4-isobutoxy-1H-indole-2-carboxylic acid [1-(1-methyl-piperidin-3-ylmethyl)-piperidin-4-yl]-amide



This compound is synthesized from the compound 161 (see example 127) and (1-Methyl-piperidin-3-yl)-methanol analogously to the method described in Example 127.
Yield: 60 mg (50%). MS (ESI): 427 $[M+H]^+$,1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, NH), 8.18(d, NH), 7.21 (s, 1H), 7.02 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 3,85 (d, 2H), 3.75 (m, 1H), 2.88 (m, 1H), 2,78 (m, 2H), 2.62 (m, 1H), 2.12 (s, 3H), 2.13-2.05 (m,3H), 2.00-1.84 (m, 2H), 1.84-1.40 (m, 10H), 1.05 (d, 6H), 0.82 (m, 1H).

Example 129

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide, 162 (preparation see below) and (1R,9aR)-1-(octahydro-quinolizin-1-yl)-methanol analogously to the method described in example 127.
MS (ESI): 479.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.2 (d, 1H), 7.2 (d, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.04 (d, 2H), 3.76 (m, 1H), 2.6-2.9 (m, 5H), 2.22-2.54 (m, 2H), 1.06-2.17 (m, 26H).

Synthesis of 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide, 162.

(1) **Step A:4-[(4-Cyclobutylmethoxy-1H-indole-2-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester, 163**

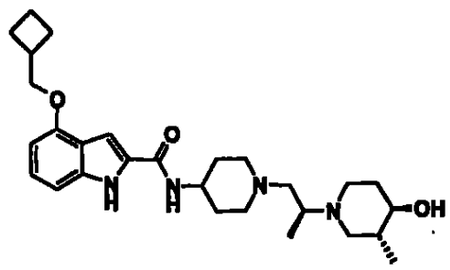
To a solution of 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid (62) from example 34 (2.2 g, 8.97 mmol) in 20 ml of DCM is added 4-amino-piperidine-1-carboxylic acid tert-butyl ester (1.98 g, 9.87 mmol), HOBT (1.37 g, 8.97 mmol), triethylamine (2.5 ml, 17.94 mmol) and EDC (1.72 g, 8.97 mmol). The mixture is stirred at room temperature over night. It is then washed with 2N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated to give a yellow powder. The crude material is purified by chromatography on silicagel using hexane and EtOAc (from 0% to 20%).
Yield: 3.02 g (79%). MS (ESI): 426.3 [M-H]$^-$, 1H-NMR ($CDCl_3$): δ (ppm) 9.33 (s, 1H), 7.17 (t, 1H), 7.03 (d, 1H), 6.97 (s, 1H), 6.5 (d, 1H), 6.12 (d, 1H), 4.13 (m, 4H), 4.07 (d, 2H), 2.78-2.97 (m, 4H), 1.88-2.25 (m, 8H), 1.46 (s, 9H).

(2) **Step B: 4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide, 162**

The tert-butyl ester (163) from above (3.02 g, 7.05 mmol) is dissolved in 20 ml of dioxane. A 4M-solution of HCl in dioxane (14.1 ml, 56.4 mmol) is added and the mixture is stirred for 24 hours. Evaporation gave the hydrochloride as a white powder.
Yield: 2.93 g (>100%, not completely dry).
MS (ESI): 328.2 [M+H]$^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.59 (s, 1H), 8.75 (br m, 2H), 8.51 (d, 1H), 7.25 (s, 1H), 7.07 (t, 1H), 6.99 (d, 1H), 6.5 (d, 1H), 4.1 (m, 1H), 4.05 (d, 2H), 3.25-3.45 (m, 2H), 3.02 (m, 2H), 2.78 (m, 1H), 2.14 (m, 2H), 1.85-2.04 (m, 5H), 1.76 (m, 2H).

Example 130

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3R,4R)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide, 162 (see example 129) and 2,2-dimethyl-propionic acid (3R,4R)-1-((R)-2-hydroxy-propyl)-3-methyl-piperidin-4-yl ester, 164 (preparation see below) analogously to the method described in example 127, followed by pivaloyl cleavage as described for amine 55.

MS (ESI): 483.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (br s, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.44 (m, 1H), 4.04 (d, 2H), 3.73 (m, 1H), 2.58-2.96 (m, 7H), 2.04-2.41 (m, 6H), 1.83-2.02 (m, 6H), 1.66-1.82 (m, 3H), 1.45-1.65 (m, 2H), 1.2-1.44 (m, 2H), 0.91 (d, 3H), 0.86 (d, 3H).

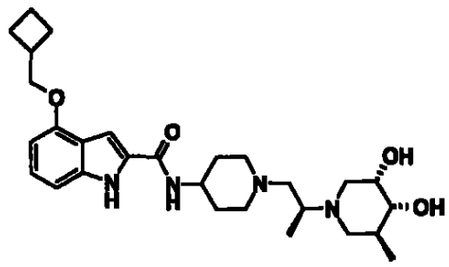
(1) **2,2-Dimethyl-propionic acid (3R,4R)-1-((R)-2-hydroxy-propyl)-3-methyl-piperidin-4-yl ester (164)**

A solution of piperidine 20 (3 g, 15.05 mmol) and (R)-2-methyl-oxirane (15.05 ml, 150.5 mmol) in 10 ml of ethanol is stirred for 24 hours in a closed flask. The solvent is evaporated and the residue distilled in a Kugelrohr apparatus (0.08 mbar, 80-90C).

Yield: 3.82 g (99%). MS (ESI): 258.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 4.34 (br s, 1H), 4.24 (td, 1H), 3.70 (sextett, 1H), 2.79 (m, 2H), 2.03-2.28 (m, 3H), 1.65-1.9 (m, 3H), 1.45 (qd, 1H), 1.14 (s, 9H), 1.02 (d, 3H), 0.81 (d, 3H), $[\alpha]_D$ = -66.1 (c=1.5 in MeOH)

Example 131

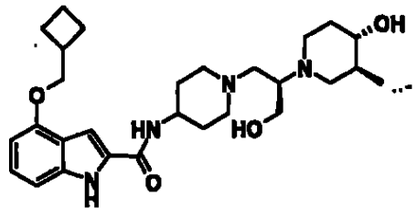
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4R,5S)-3,4-dihydroxy-5-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide, 162 (see example 129) and amine 35 analogously to the method described in 54, followed by cleavage of the protecting group.
MS (ESI): 499.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.28 (br s, 1H), 7.23 (s, 1H), 7.04 (t, 1H), 6.99 (d, 1H), 6.49 (d, 1H), 4.07 (m, 1H), 4.06 (d, 2H), 4.02 (m, 1H), 3.76 (m, 1H), 3.55 (m, 1H), 2.58-2.96 (m, 6H), 2.25-2.4 (m, 3H), 1.83-2.15 (m, 11H), 1.66-1.82 (m, 2H), 1.45-1.65 (m, 2H), 0.91 (d, 3H), 0.86 (d, 3H).

Example 132

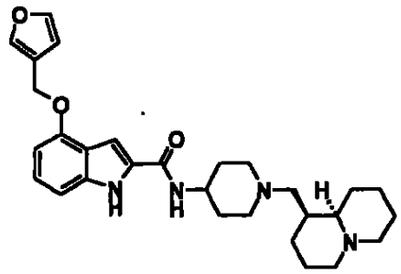
4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(R)-3-hydroxy-2-((3S,4S)-4-ydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-cyclobutylmethoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide, 162 (see example 129) and 2,2-dimethyl-propionic acid (3S,4S)-1-((S)-2-hydroxy-3-trityloxy-propyl)-3-methyl-piperidin-4-yl ester (60) analogously to the method described in 56, followed by subsequent removal of the protection groups with sodium methylate and 80% acetic acid.
MS (ESI): 499.5 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.22 (d, 1H), 7.2 (d, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.45 (d, 1H), 4.28 – 4.45 (m, 1H), 4.04 (d, 2H), 3.7 – 3.8 (m, 1H), 3.42 (d, 2H), 2.6 – 2.96 (m, 7H), 2.25 - 2.42 (m, 2H).1.15 – 2.16 (m, 16H), 0.86 (d, 3H).

Example 133

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide, 165 (preparation see below) and (1R,9aR)-1-(octahydro-quinolizin-1-yl)-methanol analogously to the method described in example 127.
MS (ESI): 491.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.13 (d, 1H), 7.82 (s, 1H), 7.68 (t, 1H), 7.22 (d, 1H), 7.05 (t, 1H), 6.98 (d, 1H), 6.62 (s, 1H), 6.59 (d, 1H), 5.03 (s, 2H), 3.74 (m, 1H), 2.8 (m, 2H), 2.69 (m, 2H), 2.43-2.53 (m, 1H), 2.27 (m, 1H), 2.02 (m, 1H), 1.07-1.95 (m, 19H).

Synthesis of 4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (165)

(1) Step A: 4-{[4-(Furan-3-ylmethoxy)-1H-indole-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (166)

To a solution of 4-(furan-3ylmethoxy)-1H-indole-2-carboxylic acid (95) from Example 33 (5 g, 19.44 mmol) in 10 ml of DCM is added 4-amino-piperidine-1-carboxylic acid tert-butyl ester (3.89 g, 19.44 mmol), HOBT (2.98 g, 19.44 mmol), triethylamine (5.4 ml, 38.88 mmol) and EDC (3.73 g, 19.44 mmol). The mixture is stirred at room temperature over night. It is then washed with 2N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated to give a yellow powder. The crude material is purified by chromatography on silicagel using DCM and EtOAc (from 0% to 10%).

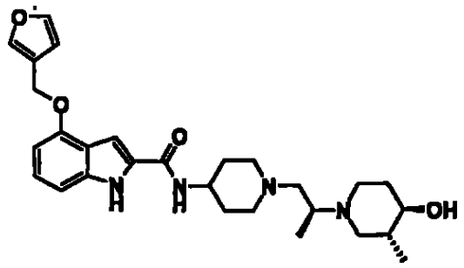
Yield: 7.51 g (88%). MS (ESI): 438.3 [M-H]⁻, 1H-NMR ($CDCl_3$): δ (ppm) 9.42 (s, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.21 (t, 1H), 7.05 (d, 1H), 6.96 (s, 1H), 6.6 (d, 1H), 6.55 (s, 1H), 6.08 (d, 1H), 5.07 (d, 2H), 4.04-4.2 (overlapping m, 3H), 2.91 (m, 2H), 2.01 (m, 2H), 1.48 (s, 9H) 1.42 (m, 2H).

(2) **Step B: 4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (165)**

The tert-butyl ester (166) from above (695 mg, 1.58 mmol) is dissolved in 5 ml of dioxane. A 4M-solution of HCl in dioxane (3.2 ml, 12.8 mmol) is added and the mixture is stirred for 24 hours. Evaporation gave the hydrochloride as a white powder.
Yield: 595 mg (100%). MS (ESI): 340.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 9.0 (br m, 2H), 8.5 (d, 1H), 7.85 (s, 1H), 7.71 (s, 1H), 7.3 (s, 1H), 7.09 (t, 1H), 7.02 (d, 1H), 6.62 (d, 1H), 6.64 (s, 1H), 5.05 (d, 2H), 4.07 (m, 1H), 3.31 (m, 2H), 3.0 (m, 2H), 1.96 (m, 2H), 1.78 (m, 2H).

Example 134

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3R,4R)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

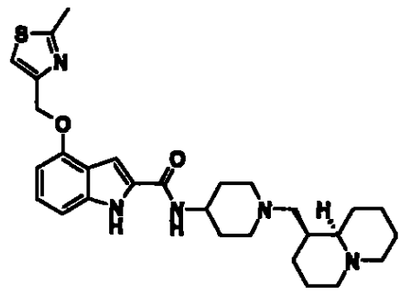


This compound is synthesized from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide, 165 (see example 133) and 2,2-dimethyl-propionic acid (3R,4R)-1-((R)-2-hydroxy-propyl)-3-methyl-piperidin-4-yl ester, 164 (preparation see example 130) analogously to the method described in example 127, followed by pivaloyl cleavage as described for amine 55.
MS (ESI): 495.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (br s, 1H), 7.23 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.82 (s, 1H), 6.6 (d, 1H), 5.03 (s,

2H), 4.43 (d, 1H), 3.72 (m, 1H), 2.58-2.95 (m, 5H), 2.32 (m, 1H), 2.24 (m, 1H), 2.04-2.19 (m, 2H), 1.9 (m, 2H), 1.67-1.79 (m, 3H), 1.43-1.81 (m, 2H), 1.21-1.41 (m, 3H), 0.91 (d, 3H), 0.86 (d, 3H).

Example 135

4-(2-Methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide



This compound is synthesized from 4-(2-methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide, (167, preparation see below) and (1R,9aR)-1-(octahydro-quinolizin-1-yl)-methanol analogously to the method described in example 127.
MS (ESI): 522 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.15 (d, 1H), 7.57 (s, 1H), 7.25 (s, 1H), 7.05 (dd, 1H), 6.98 (d, 1H), 6.62 (s, 1H), 5.18 (s, 2H), 3.74 (m, 1H), 2.8 (m, 2H), 2.69 (m, 2H), 2.68 (s, 3H), 2.43-2.53 (m, 1H), 2.27 (m, 1H), 2.02 (m, 1H), 1.07-1.95 (m, 19H).

Synthesis of 4-(2-methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (167)

(1) Step A: (2-Methyl-thiazol-4-yl)-methanol (168)

2-Methyl-thiazole-4-carboxylic acid ethyl ester (966 mg, 5.64 mmol) is dissolved in 5 ml of diethylether and cooled to -78°C. A 1M solution of lithium aluminium hydride in THF (16.9 ml, 16.9 mmol) is added dropwise and the mixture is stirred for 3.5h at -78°C. The mixture is quenched at this temperature with a saturated solution of sodium sulphate and is allowed to warm up to room temperature, followed by extraction with ether and evaporation.

Yield: 670 mg (92%). MS (ESI): 130.0 [M-H]$^-$, 1H-NMR ($CDCl_3$): δ (ppm) 7.20 (s, 1H), 5.27 (dd, 1H), 4.50 (d, 2H), 2.62 (s, 3H).

(2) **Step B: 4-(2-Methyl-thiazol-4-ylmethoxy)-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (169)**

(2-Methyl-thiazol-4-yl)-methanol (168, 670 mg, 5.2 mmol) is dissolved in 12 ml of dry THF under argon, followed by addition of 4-Hydroxy-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (102, see example 42, 1.58 g, 5.2 mmol), triphenylphosphine (1.63 g, 6.2 mmol).) and the solution is cooled to 0°C. A 40% solution of ethyl azadicarboxylate in toluene (2.7 ml, 6.2 mmol) is added dropwise and the mixture is stirred for 2.5 h at 0°C. The the solvents are removed under reduced pressure and the residue is dissolved in ethyl acetate and washed with sodiumhydrogencarbonate solution and brine. The organic layers are drid over sodium sulphate, filtrated and evaporated. The crude product is purified by flash chromatography (silica gel, ethyl acetate / hexanes 3:7)
Yield: 1.75 g (81%). MS (ESI): 417.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 7.67 (s, 1H), 7.55 (d, 1H), 7.41 (dd, 1H), 7.27 (s, 1H), 6.99 (d, 1H), 5.27 (s, 2H), 4.31 (q, 2H), 2.68 (s, 3H), 1.57 (s, 9H), 1.32 (t, 3H).

(3) **Step C: 4-(2-Methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid (170)**

4-(2-Methyl-thiazol-4-ylmethoxy)-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (169) (1.75 g, 4.2 mmol) is dissolved in 20 ml of ethanol. After addition of a 0.5M aqueous sodium hydroxide solution (33.6 ml, 16.8 mmol) the solution is heated to 60°C and stirred at this temperature for 18h. Then the reaction mixture is evaporated and the residue is dissolved in ethyl acetate. AT 0°C conc HCl is added until a pH of 1 is reached. The organic phase is washed with water and brine. The organic layers are dried over over sodium sulphate, filtrated. The product crystallized upon evaporation and could be filtrated off.
Yield: 1.21 g (100%). MS (ESI): 289.0 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.76 (br s, 1H), 7.62 (s, 1H), 7.14 (dd, 1H), 7.07 (s, 1H), 7.02 (d, 1H), 6.66 (d, 1H), 5.22 (s, 2H), 2.68 (s, 3H).

(4) **Step D: 4-{[4-(2-Methyl-thiazol-4-ylmethoxy)-1H-indole-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (171)**

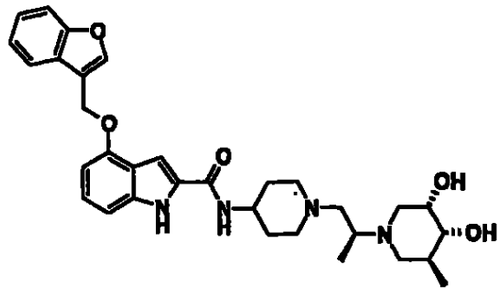
4-(2-Methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid (170) (1.21 g, 4.2 mmol) is dissolved in 10 ml of DMF and the solution is cooled to 0°C. After addition of Huenige base (2.16 ml, 12.6 mmol), piperidin-4-yl-carbamic acid tert-butyl ester (3) (841 mg, 4.2 mmol) and PyBOP (2.4 g, 4.6 mmol) the mixture is stirred at room temperature for 16h. Ethyl acetate is added follwed by concentrated sodium hydroxide, until a pH of 11 is reached. The organic layer is washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The crude product is purified by flash-chromatography (silica gel, ethyl acetate / cyclohexane 1:1).
Yield: 1.58 g (80%). MS (ESI): 471.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.58 (br s, 1H), 8.25 (d, 1H), 7.61 (s, 1H), 7.27 (s, 1H), 7.09 (dd, 1H), 7.02 (d, 1H), 6.63 (d, 1H), 5.18 (s, 2H), 3.93 (m, 3H), 2.85 (m, 2H), 2.69 (s, 3H), 1.78 (m, 2H), 1.4 (s, 9H), 1.38 (m, 2H).

(5) **Step E: 4-(2-Methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (167)**

171 from above (1.58 g, 3.36 mmol) is dissolved in a 4M solution of HCl in dioxane (32 ml, 128 mmol) and stirred for 45 min at room temperature. Then the reaction mixture is evaporated, dissolved in ethyl acetate and conc sodium hydroxide is added until a pH of 11 is reached. The organic layer is washed with brine, dried over sodium sulphate and evaporated under reduced pressure.
Yield: 1.28 g (100%). %). MS (ESI): 371.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.56 (br, 1H), 8.28 (d, 1H), 7.61 (s, 1H), 7.3 (s, 1H), 7.09 (dd, 1H), 7.02 (d, 1H), 6.62 (d, 1H), 5.19 (s, 2H), 3.90 (m, 1H), 3.07 (m, 2H), 2.70 (s, 3H), 2.62 – 2.75 (m, 2H), 1.72 – 1.85 (m, 3H), 1.4 – 1.55 (m, 2H).

Example 136

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(3,4-dihydroxy-5-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide, 172 (preparation see below) and amine 35 analogously to the method described in 54, followed by cleavage of the protecting group.
MS (ESI): 561 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.16 (s, 1H), 8.15 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (dd, 1H), 7.29 (dd, 1H), 7.19 (s, 1H), 7.09 (dd, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.04 (d, 1H), 3.98 (m, 1H), 3.72 (m, 1H), 3.53 (m, 1H), 2.50-2.90 (m, 7H), 2.24-2.38 (m, 2H), 1.88-2.08 (m, 3H), 1.66-1.78 (m, 3H), 1.45-1.58 (m, 2H), 0.88 (d, 3H), 0.83 (d, 3H).

Synthesis of 4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (172)

(1) Step A: 4-[[4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carbonyl]-amino]-piperidine-1-carboxylic acid tert-butyl ester (173)

To a ice-cold solution of 4-(benzofuran-3ylmethoxy)-1H-indole-2-carboxylic acid (105, see example 50) (200 mg, 0.651 mmol) in 2 ml of dimethylformamide is added Huenigs base (334 ul, 1.95 mmol). After stirring at 0°C for 10 min, 4-amino-piperidine-1-carboxylic acid tert-butyl ester (130 mg, 0.651 mmol) and PyBOP (356 mg, 0.684 mmol) are added subsequently. The mixture is stirred at room temperature over night. It is then diluted with ethyl acetate, washed with 1N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated to give 980 mg of a lightbrown oil. The crude material is purified by chromatography on silicagel using cyclohexane and ethylacetate (1:1).
Yield: 318 mg (100%). MS (ESI): 488.2 $[M-H]^-$, 1H-NMR ($CDCl_3$): δ (ppm) 9.15 (s, 1H), 7.77 (s, 1H), 7.72 (d, 1H), 7.55 (d, 1H), 7.38 (dd, 1H), 7.3 (dd, 1H), 7.23 (d, 1H), 7.08 (d, 1H),

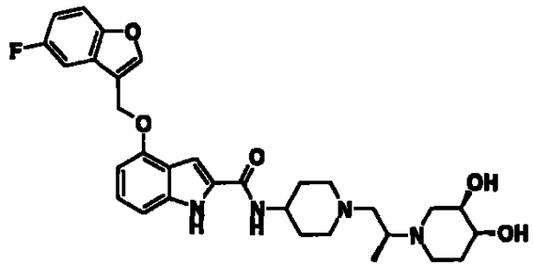
6.91 (s, 1H), 6.7 (d, 1H), 5.96 (d, 1H), 5.34 (s, 2H), 4.04-4.2 (overlapping m, 3H), 2.91 (m, 2H), 2.01 (m, 2H), 1.48 (s, 9H), 1.40 (m, 2H).

(2) **Step B: 4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (172)**

The tert-butyl ester (173) from above (318 mg, 0.65 mmol) is dissolved in a 4M-solution of HCl in dioxane (6 ml, 1.2 mmol) and stirred for 1 hour at room temperature. Evaporation gave the hydrochloride as a white powder, which is dissolved in water, treated with conc NaOH solution at 0°C to an pH of 11 and extracted with ethyl acetate. The organic layers are washed with brine, dried over sodium sulphate and evaporated.
Yield: 248 mg (98%) of a light yellow solid. MS (ESI): 390.2 $[M+H]^+$.

Example 137

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(3,4-dihydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (174, preparation see below) and amine 34 analogously to the method described for 54, followed by cleavage of the protecting group.
MS (ESI): 585 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.52 (s, 1H), 8.28 (s, 1H), 7.88 (dd, 1H), 7.52 (d, 1H), 7.23 (s, 1H), 7.21 (dd, 1H), 7.11 (dd, 1H), 7.03 (d, 1H), 6.72 (d, 1H), 5.35 (s, 2H), 4.19 (m, 1H), 4.13 (d, 1H), 3.73 (m, 1H), 3.52 (br s, 1H), 3.44 (br s, 1H), 2.9 (m, 3H), 2.52 (m, 2H), 2.33 (m, 3H), 2.11 (m, 1H), 2.03 (dd, 1H), 1.84 (dd, 1H), 1.75 (d, 1H), 1.45 – 1.65 (m, 5H), 0.9 (d, 3H).

~~100~~ 120 179

Synthesis of 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (174)

(1) **Step A: 4-{[4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (175)**

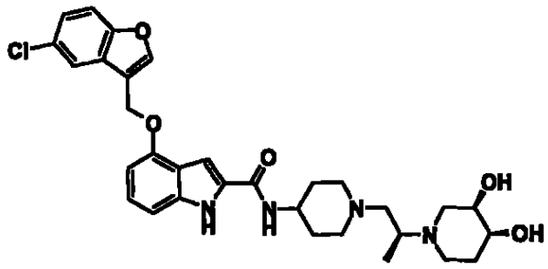
To a solution of 4-(5-fluoro-benzofuran-3ylmethoxy)-1H-indole-2-carboxylic acid (113, see example 60, 160 mg, 0.49 mmol) is dissolved in 1.5 ml of DMF and cooled to 0°C. After addition of Huenigs base (252 ul, 1.5 mmol) the mixture is stirred for 15min, then piperidin-4-yl-carbamic acid tert-butyl ester (3, 98.5 mg, 0.49 mmol) is added, followed by PyBOP (269 mg, 0.51 mmol). The mixture is stirred at room temperature for 16h. Then the mixture is diluted with ethyl acetate, washed 1N sodium hydroxide solution and brine. The organic layers are dried over sodium sulfate and evaporated under reduced pressure. The crude product (581 mg) is purified by flash-chromatography (silica gel, cyclohexane / ethyl acetate 1:1)
Yield: 250 mg (100%). MS (ESI): 506.2 $[M-H]^-$.

(2) **Step B: 4-(5-fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (174)**

The tert-butyl ester (175) from above (250 mg, 0.49 mmol) is dissolved in a 4M-solution of HCl in dioxane (4 ml, 16 mmol) and the mixture is stirred for 1h at room temperature. Evaporation gave the hydrochloride as a yellow solid, which is dissolved in 5 ml of water and the pH is adjusted to 11 by addition of conc sodium hydroxide. The solution is extracted with ethyl acetate, the organic layers are washed with brine and dried over sodium sulphate. Evaporation gave 200 mg (100%) of a white solid. %).
MS (ESI): 408.2 $[M+H]^+$.

Example 138

4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(3,4-dihydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide,(176, preparation see below) and amine 34 analogously to the method described for 54, followed by cleavage of the protecting group.
MS (ESI): 581 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (br s, 1H), 8.28 (s, 1H), 8.17 (d, 1H), 7.79 (s, 1H), 7.68 (d, 1H), 7.39 (d, 1H), 7.22 (s, 1H), 7.10 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.36 (s, 2H), 4.18 (m, 1H), 4.12 (d, 1H), 3.72 (m, 1H), 3.52 (m, 1H), 3.45 (m, 1H), 2.45 – 2.9 (m, 4H), 2.33 (m, 4H), 1.88 – 2.14 (m, 3H), 1.73 (m, 2H), 1.42 – 1.65 (m, 4H), 0.89 (d, 3H).

Synthesis of 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (176)

(1) **Step A: 4-{[4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (177)**

This compound is synthesized from 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (113, see example 60) and amine 3 analogously to the method described for 175.
Yield: 270 mg (60%). MS (ESI): 522 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.58 (m, 1H), 8.28 (s, 1H), 8.20 (d, 1H), 7.8 (s, 1H), 7.69 (d, 1H), 7.4 (d, 1H), 7.2 (s, 1H), 7.11 (dd, 1H), 7.03 (d, 1H), 6.72 (d, 1H), 5.36 (s, 2H), 3.93 (m, 3H), 2.7 – 2.9 (m, 2H), 1.76 (d, 2H), 1.4 (s, 9H), 1.29-1.42 (m, 2H).

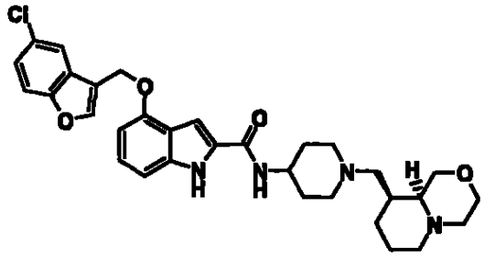
(2) **Step B: 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (176)**

This compound is synthesized from 177 analogously to the method described for 175.

MS (ESI): 424.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.38 (s, 1H), 8.14 (s, 1H), 8.02 (d, 1H), 7.66 (s, 1H), 7.55 (d, 1H), 7.27 (d, 1H), 7.09 (s, 1H), 6.98 (dd, 1H), 6.91 (d, 1H), 6.59 (d, 1H), 5.23 (s, 2H), 3.68 (m, 1H), 2.8 (m, 1H), 2.37 (m, 3H), 1.57 (m, 1H), 1.25 (m, 3H).

Example 139

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(9S,9aS)-1-(octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)methyl]-piperidin-4-yl}-amide

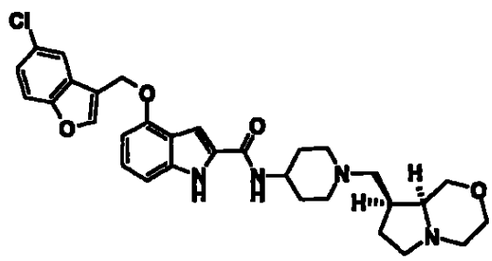


This compound is synthesized from the compound 176 (see example 138) and (9RS,9aSR)-1-(octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)-methanol (63) analogously to the method described in example 127.

Yield: 7.7 mg (12%) of a white solid. MS (ESI): 575/577 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.11 (d, 1H), 7.78 (d, 1H), 7.67 (d, 1H), 7.38 (dd, 1H), 7.18 (d, 1H), 7.10 (m, 1H), 7.03 (d, 1H), 6.70 (d, 1H), 5.36 (s, 2H), 3.75-3.60 (m, 2H), 3.50-3.30 (m, 4H), 2.80-2.55 (m, 2H), 2.60-2.50 (m, 2H), 2.32 (d, 2H), 2.10-1.65 (m, 9H), 1.60-1.40 (m, 3H), 1.35-1.20 (m, 2H).

Example 140

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(8S,8aS)-1-(hexahydro-pyrrolo[2,1-c][1,4]oxazin-8-yl)methyl]-piperidin-4-yl}-amide

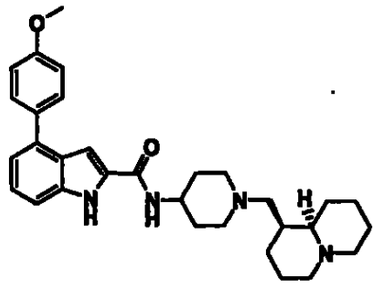


This compound is synthesized from the compound 176 (see example 136) and (9RS,9aSR)-1-(octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)-methanol (67) analogously to the method described in example 127.

Yield: 82 mg (14.6%) of a white solid. MS (ESI): 563/565 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.25 (s, 1H), 8.10 (d, 1H), 7.78 (d, 1H), 7.67 (d, 1H), 7.38 (bd, 1H), 7.19 (s, 1H), 7.10-7.00 (m, 2H), 6.70 (d, 1H), 5.35 (s, 2H), 4.00 (m, 1H), 3.90 (m, 1H), 3.75-3.60 (m, 2H), 3.40-3.30 (m, 2H), 2.95-2.70 (m, 1H), 2.40-2.20 (m, 2H), 2.10-1.70 (m, 8H), 1.55-1.25 (m, 4H), 1.15 (t, 1H), 1.07 (t, 1H).

Example 141

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



This compound is synthesized from the compound 178 (preparation see below) and octahydro-2H-chinolizin-1-ylmethanol analogously to the method described in example 127.

Yield: 350 mg (33.7%). MS (ESI): 501 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.22 (d, 1H), 7.56 (d, 2H), 7.37 (d, 1H), 7.31 (m, 1H), 7.20 (dd, 1H), 7.07 (d, 2H), 7.01 (d, 1H), 3.81 (s, 3H), 3.75 (m,1H), 3.16 (d, 1H), 2.80 (m, 2H), 2.67 (m, 2H), 2.46 (dd, 1H), 2.26 (m, 1H), 1.1-2.1 (m, 19H).

Synthesis of 4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid piperidin-4-ylamide (178):

(1) Step A: 4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid (128)

4-Bromo-1H-indole-2-carboxylic acid (5 g, 20.8 mmol) and 4-methoxy-phenyl-boronic acid (3.2 g, 20.8 mmol) are dissolved in 1-propanol (100 ml) and the mixture is flushed with argon for 30 min. Then bis(triphenylphosphin)palladium(II)chloride (200 mg, 1 mmol) and Na2CO3 (4.4 g, 40.2 mmol) are added and the reaction mixture is stirred at 85°C for 3h. After cooling down to room temperature, ethyl acetate and 2M HCl are added. The organic layers are dried over sodium sulphate. Evaporation gave 6 g of an beige solide, which is further purified by crystallisation from ethyl acetate.
Yield: 4.7 g (84%). MS (ESI): 266 [M-H]⁻.

(2) Step B: 4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (179)

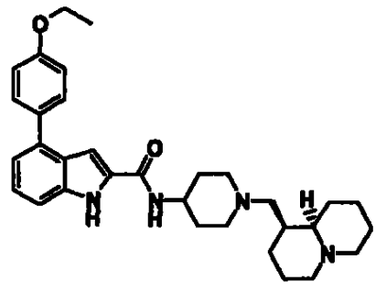
128 (4.7 g, 17.6 mmol) and 1-benzyl-piperidin-4-ylamine (3.3 g, 17.6 mmol) are dissolved in DMF (70 ml) and after addition of TBTU (6.4 g, 19.4 mmol) and ethyldiisopropylamine (12 ml, 70.4 mmol) the mixture is stirred at room temperature for 2h. Then the solvent is evaporated at high vacuum. The residue is dissolved in ethyl acetate washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layers are dried over sodium sulfate and evaporated under reduced pressure. The crude mixture is crystallized from methanol.
Yield: 4.1 g (53%). MS (ESI): 440 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.26 (d, 1H), 7.56 (d, 2H), 7.38 (d, 1H), 7.15 – 7.35 (m, 7H), 7.08 (d, 2H), 7.01 (d 1H), 4.07 (m, 1H), 3.81 (s, 3H), 3.47 (s, 2H), 2.8 (m, 2H), 2.04 (m, 2H), 1.77 (m, 2H), 1.58 (m, 2H).

(3) Step C: 4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid piperidin-4-ylamide (178)

179 (4 g, 9.1 mmol) is dissolved in 100 ml of methanol, flushed with argon and, after addition of Pd-C (100 mg) and 2M HCl (5.5 ml, 11 mmol), the mixture is hydrogenated at room temperature for 3h. The mixture is filtrated over celite and evaporated.
Yield: 1 g of a white solid (29%). MS (ESI): 350 $[M+H]^+$.

Example 142

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



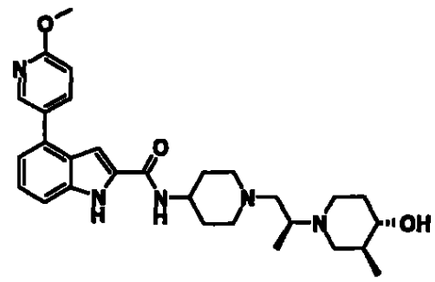
This compound is synthesized from the compound 180 (preparation see below) and octahydro-2H-chinolizin-1-ylmethanol analogously to the method described in example 127.
Yield: 23 mg (16.2 %). MS (ESI): 515 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.67 (s, 1H), 8.28 (d, 1H), 7.56 (d, 2H), 7.33 (d, 1H), 7.3 (m, 1H), 7.20 (dd, 1H), 7.0 - 7.07 (m, 3H), 4.08 (q, 2H), 3.77 (m,1H), 2.80 (dd, 2H), 2.67 (m, 2H), 2.46 (dd, 1H), 2.28 (dd, 1H), 2.01 (dd, 1H), 1.36 (t, 3H), 1.1-2.1 (m, 19H).

Synthesis of 4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid piperidin-4-ylamide (180):

This compound has been synthesized from 4-ethoxy-phenyl-boronic acid analogously to the method described in the synthesis of 178 (see example 141).
MS (ESI): 364 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.64 (s, 1H), 8.28 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.31 (s, 1H), 7.19 (dd, 1H), 7.06 (d, 2H), 7.02 (d, 1H), 4.09 (q, 2H), 3.81 (m, 1H), 3.4 (m, 1H), 2.92 (m, 2H), 2.46 (m, 2H), 1.77 (m, 2H), 1.4 (m, 2H), 1.37 (t, 3H).

Example 143

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide



This compound is synthesized from 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid piperidin-4-ylamide (181, preparation see below) and amine 164 analogously to the method described for 54, followed by cleavage of the protecting group.
MS (ESI): 504 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.48 (br s, 1H), 8.28 (d, 1H), 7.97 (d, 1H), 7.41 (d, 1H), 7.36 (s, 1H), 7.24 (dd, 1H), 7.09 (d, 1H), 6.96 (d, 1H), 4.44 (d, 1H), 3.93 (s, 3H), 3.68 – 3.82 (m, 1H), 2.61 – 2.96 (m, 6H), 2.04-2.39 (m, 4H), 1.85-1.96 (m, 2H), 1.66-1.82 (m, 3H), 1.45-1.65 (m, 2H), 1.2-1.44 (m, 2H), 0.91 (d, 3H), 0.86 (d, 3H).

Synthesis of 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid piperidin-4-ylamide (181)

(1) Step A: 4-[(4-Bromo-1H-indole-2-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (182)

4-Bromo-1H-indole-2-carboxylic acid (3 g, 12.5 mmol) is dissolved in 30 ml of DMF and the solution is cooled to 0°C. After addition of Huenigs base (6.4 ml, 37.5 mmol), the mixture is stirred for 15 min. Then piperidin-4-yl-carbamic acid tert-butyl ester 3 (2.5 g, 12.5 mmol) is added, followed by PyBOP (7.2 g, 13.7 mmol). The reaction mixture is stirred for 18 h at room temperature. Then ethyl acetate is added and conc sodium hydroxide until a pH of 11 is reached. The organic layers are washed with brine, dried over sodium sulphate and evaporated. The crude product is further purified by flash-chromatography (silica gel, ethyl acetate / cyclohexane 1:1)

Yield: 5.13 g (97%). MS (ESI): 420, 422 [M-H]$^-$, 1H- NMR (DMSO-d_6): δ (ppm) 11.9 (m, 1H), 8.48 (d, 1H), 7.45 (d, 1H), 7.27 (d, 1H), 7.21 (s, 1H), 7.11 (dd, 1H), 2.86 (m, 2H), 1.81 (m, 2H), 1.42 (s, 9H), 1.42 (m, 2H).

(2) **Step B: 4-{[4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (183)**

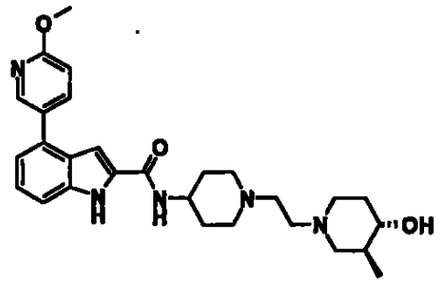
An argon stream is bubbled through a solution of 182 from above (500 mg, 1.2 mmol) and 2-methoxy-5-pyridine boronic acid (181 mg, 1.2 mmol) in 4 ml of 1-propanol for 15 min. Then 2M aqueous sodium carbonate solution (1.2 ml, 2.4 mmol) and bis(triphenylphosphine)palladium-(II)-chloride (50 mg, 0.07mmol) are added and the reaction mixture is stirred at 85°C for 3h. Then the mixture is cooled to 0°C and ethyl acetate andconcentrated sodium hydroxide solution is added until a pH of 11 is reached. The solution is washed with brine and the organic layers are dried over sodium sulfate and evaporated. The crude product is purified by flash-chromatography (silica gel, cyclohexane / ethyl acetate 7:3).
Yield: 290 mg (69%). MS (ESI): 451.2 [M+H]$^+$, 1H-NMR ($CDCl_3$): δ (ppm) 9.3 (s, 1H), 8.53 (s, 1H), 7.96 (d, 1H), 7.46 (d, 1H), 7.38 (dd, 1H), 7.17 (d, 1H), 6.98 (s, 1H), 6.86 (d, 1H), 6.12 (d, 1H), 4.13 (m, 2H), 4.08 (s, 3H), 2.91 (m, 2H), 2.01 (m, 2H), 1.48 (s, 9H) 1.42 (m, 2H), 1.27 (m, 1H).

(3) **Step C: 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid piperidin-4-ylamide (181)**

183 from above (370 mg, 0.82 mmol) is dissolved in a 4M solution of HCl in dioxane (7.5 ml, 30 mmol) and stirred for 1 h at room temperature. Then the reaction mixture is evaporated, dissolved in ethyl acetate and conc sodium hydroxide is added until a pH of 11 is reached. The organic layer is washed with brine, dried over sodium sulphate and evaporated under reduced pressure.
Yield: 300 mg (100%). MS (ESI): 351.2 [M+H]$^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.74 (m, 1H), 8.51 (s, 1H), 8.35 (d, 1H), 8.00 (d, 1H), 7.44 (d, 1H), 7.41 (s, 1H), 7.27 (dd, 1H), 7.11 (d, 1H), 7.00 (d, 1H), 3.95 (s, 3H), 3.84 (m, 1H), 2.96 (m, 2H), 2.31 (m, 1H), 2.01 (m, 2H), 1.75 (m, 2H), 1.4 (m, 2H).

Example 144

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



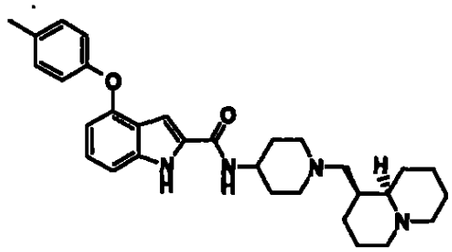
This compound is synthesized from 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide (184, preparation see below) and 2,2-Dimethyl-propionic acid (3S,4S)-3-methyl-piperidin-4-yl ester (17) analogously to the method described in example 150, followed by cleavage of the protecting group.
MS (ESI): 492 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.70 (s, 1H), 8.48 (br s, 1H), 8.30 (d, 1H), 7.97 (dd, 1H), 7.42 (d, 1H), 7.36 (s, 1H), 7.24 (t, 1H), 7.09 (d, 1H), 6.97 (d, 1H), 4.47 (d, 1H), 3.92 (s, 3H), 3.75 (m, 1H), 2.70 -2.90 (m, 5H), 2.31 - 2.41 (m, 4H), 1.86 - 2.04 (m, 3H), 1.66 - 1.82 (m, 3H), 1.46 - 1.62 (m, 3H), 1.3 - 1.44 (m, 2H), 0.86 (d, 3H).

Synthesis of 4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide (184)

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid piperidin-4-ylamide (181), 150 mg, 0.43 mmol) is dissolved in 3 ml of ethanol under argon. After addition of sodium carbonate (182 mg, 1.7 mmol) and 2-bromo-ethanol (61 ul, 0.85 mmol), the reaction mixture is stirred at 80°C for 13h. The mixture is diluted with methylene chloride, filtrated and the filtrate is evaporated. Evaporation under reduced pressure gave 128 mg of crude product, which is further purified by Flash-chromatography (dichloro methane / methanol / 25% ammonia (90:9:1). Yield: 90 mg (53%). MS (ESI): 395.2 $[M+H]^+$.

Example 145

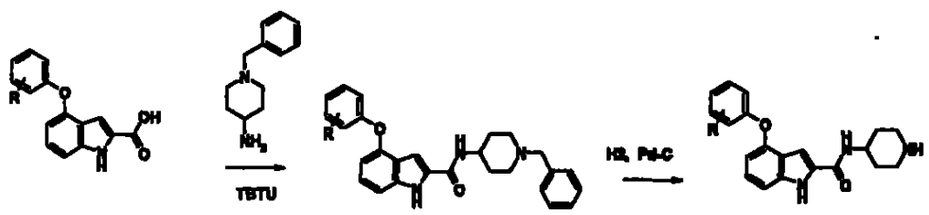
4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide



This compound is synthesized from the compound 185 (preparation see below) and octahydro-2H-chinolizin-1-ylmethanol analogously to the method described in example 127. Yield: 88 mg (34.9%). MS (ESI): 501 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.2 (d, 2H), 7.15 (d, 2H), 7.1 (s, 1H), 6.85 (d, 2H), 6.47 (d, 1H), 3.72 (m, 1H), 2.8 (dd, 2H), 2.70 (d, 2H), 2.45 (m, 1H), 2.3 (s, 3H), 2.28 (m, 1H), 2.03 (dd, 1H), 1.1 - 2.1 (m, 19H).

Synthesis of 4-p-tolyloxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (185):

Reaction Scheme 18:



(1) Step A: 4-p-tolyloxy-1H-indole-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (186)

4-p-tolyloxy-1H-indole-2-carboxylic acid (137) (850 mg, 3.2 mmol) and 4-amino-N-benzylpiperidine (605 mg, 3.2 mmol) are dissolved in 5 ml of DMF and after addition of TBTU (1.2 g, 3.5 mmol) and ethyldiisopropylamine (2.2 ml, 12.8 mmol) the mixture is stirred

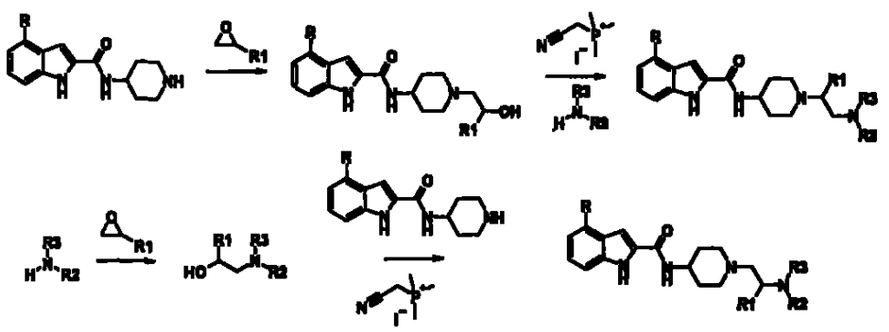
at room temperature for 2h. Then the mixture is evaporated at high vacuum. The residue is dissolved in ethyl acetate and washed with saturated NaHCO3-solution and brine. The organic layers are dried over Na2SO4, filtrated and evaporated under reduced pressure. Yield: 1.47g (100%) of a yellow foam. MS (ESI): 438 [M-H]⁻.

(2) Step B: 4-p-Tolyloxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (185)

Pd-C (1g) is placed intoa flask filled with argon and covered with methanol. 186 (1.4 g, 3.2 mmol) is dissolved in 100 ml of methanol and 1.6 ml of 2M HCl and added. After hydrogenation at room temperature for 5h the mixture is filtrated over celite and evaporated. Yield: 1.1g (96%) of a white foam. MS (ESI): 350 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.43 (d, 1H), 7.2 (d, 1H), 7.1 - 7.2 (m, 4H), 6.85 (d, 2H), 6.47 (d, 1H), 4.05 (m, 1H), 3.26 (m, 2H), 2.90 (m, 2H), 2.73 (s, 1H), 2.28 (s, 3H), 1.9 (m, 2H), 1.7 (m, 2H).

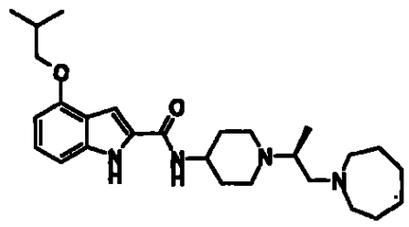
Alternatively, the branched indole-2-carboxamides could be prepared as shown in reaction scheme 19.

Reaction Scheme 19:



Example 146

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1S-methyl-ethyl)-piperidin-4-yl]-amide



(1) **Step A: 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2*R*-hydroxy-propyl)-piperidin-4-yl]-amide (187)**

A solution of the hydrochloride of 4-isobutoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (161) from Example 127 (300 mg, 0.85 mmol) in 5 ml of ethanol and triethylamine (0.472 ml, 3.4 mmol) is treated with R(+)-propylene oxide (0.59 ml, 4.25 mmol) and stirred at room temperature in a sealed vessel for 14 hours. Another portion of R(+)-propylene oxide (0.59 ml, 4.25 mmol) is added and stirring continued for 24 hours. The solvents are then evaporated. The crude is re-dissolved in DCM and washed with 2N-NaOH and brine. The organic layer is dried over anhydrous sodium sulphate and evaporated to give a white powder.

Yield: 280 mg (91%). MS (ESI): 374.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.22 (d, 1H), 7.22 (s, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.25 (br s, 1H), 3.84 (d, 2H), 3.75 (overlapping m, 2H), 2.87 (m, 2H), 1.98-2.39 (m, 5H), 1.76 (m, 2H) 1.58 (m, 2H), 1.05 (m, 9H).

(2) **Step B: 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1*S*-methyl-ethyl)-piperidin-4-yl]-amide**

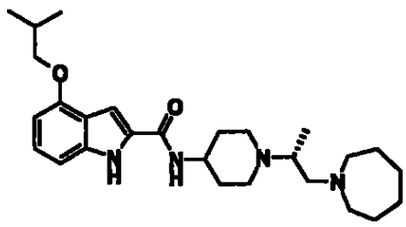
The alcohol (187) from above (100 mg, 0.27 mmol) is mixed with azepane (0.033 ml, 0.297 mmol), DIEA (0.227 ml, 1.35 mmol) and cyanomethyl-triphenyl phosphonium iodide (156 mg, 0.648 mmol) in 2 ml of propionitrile. The suspension is heated at 90 °C for 3 hours. The resulting solution is cooled, diluted with EtOAc, washed with 2N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated. The crude material is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 0% to 10%).

Yield: 74 mg (61%). MS (ESI): 455.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.22 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.44 (d, 1H), 3.84 (d, 2H), 3.72 (br m,

1H), 2.52-2.95 (m, 8H), 2.15-2.4 (m, 3H), 2.1 (m, 1H), 1.77 (m, 2H), 1.45-1.67 (m, 10H) 1.05 (d, 6H), 0.95 (d, 3H).

Example 147

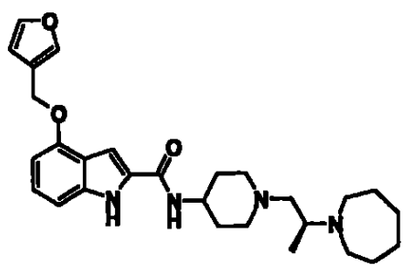
4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1*R*-methyl-ethyl)-piperidin-4-yl]-amide



The title compound is prepared as described in Example 83 from 4-isobutoxy-1H-indole-2-carboxylic acid piperidin-4-ylamide (161), S(-)-propylene oxide and azepane. Intermediate 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2*S*-hydroxy-propyl)-piperidin-4-yl]-amide (188) and final product had MS and NMR spectra identical to the (R)-enantiomers of Example 146.

Example 148

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2*S*-azepan-1-yl-propyl)-piperidin-4-yl]-amide



S(-)-propylene oxide (21.2 ml, 302.5 mmol) and azepam (3.41 ml, 30.25 mmol) are mixed in 10 ml of ethanol and stirred in a sealed vessel for 24 hours. The solvents are then

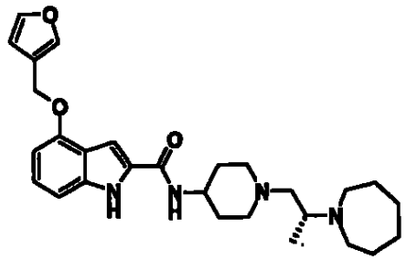
evaporated and the crude oil of 1-azepan-1-yl-propan-2*S*-ol (189) is used as such without further purification. Yield: 2.25 g (47%).

The alcohol (189) from above (83 mg, 0.405 mmol) is mixed with 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (165, see example 133) from step B (100 mg, 0.27 mmol), DIEA (0.227 ml, 1.35 mmol) and cyanomethyl-triphenyl phosphonium iodide (193 mg, 0.81 mmol) in 2 ml of propionitrile. The suspension is heated at 90 °C for 3 hours. The resulting solution is cooled, diluted with EtOAc, washed with 2N-NaOH and brine, dried over anhydrous sodium sulphate and evaporated. The crude material is purified by chromatography on silicagel using DCM (saturated with ammonia) and MeOH (from 0% to 10%).

Yield: 45 mg (35%). MS (ESI): 479.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.59 (d, 1H), 5.03 (d, 2H), 3.72 (m, 1H), 2.75-2.95 (m, 3H), 2.58 (m, 4H), 2.33 (m, 1H), 2.0-2.2 (m, 2H), 1.92 (m, 1H), 1.74 (m, 2H), 1.45-1.6 (m, 10H), 0.91 (d, 3H).

Example 149

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2*R*-azepan-1-yl-propyl)-piperidin-4-yl]-amide

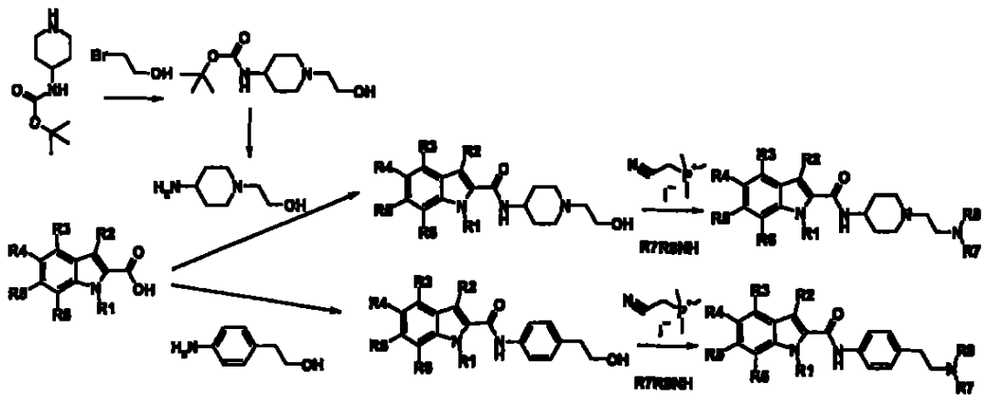


The title compound is prepared from 4-(furan-3-ylmethoxy)-1H-indole-2-carboxylic acid piperidin-4-ylamide (165) as described in Example 133 using R(+)-propylene oxide instead of the (S)-enantiomer.

MS and NMR spectra are identical to its enantiomeric example 148.

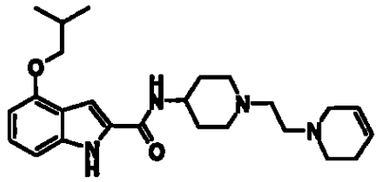
Alternatively, the 4-alkoxy-indole-2-carboxamides are prepared as shown in reaction scheme 20.

Reaction Scheme 20:



Example 150

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3,6-dihydro-2H-pyridin-1-yl)-ethyl]-piperidin-4-yl}-amide



1,2,5,6-Tetrahydropyridine (25.4 µl, 0.279 mmol), cyanomethyl-triphenyl phosphonium iodide (162.5 mg, 0.6686 mmol) and Hünig's base (171 µl, 1 mmol) are added subsequently to a suspension of 190 (preparation see below) (100 mg, 0.279 mmol) in 4 ml of propionitril. The mixture is stirred for 2h at 100°C, then diluted with ethyl acetate, washed with 1N sodium hydroxide solution and brine and dried over sodium sulfate. Evaporation gave 138 mg of crude product, which is further purified by preparative HPLC (RP, acetonitrile / water). Yield: 55 mg (47%). MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H)

3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Synthesis of 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide (190)

(1) **Step A: [1-(2-Hydroxy-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (191)**

Piperidin-4-yl-carbamic acid tert-butyl ester (5 g, 25 mmol) is dissolved in 100 ml of ethanol. After addition of sodium carbonate (10.6 g, 100 mmol), 2-bromo-ethanol (3.55 ml, 50 mmol) is added dropwise. The reaction mixture is refluxed for 16 h and then evaporated. The residue is dissolved in 100 ml of dichloromethane and filtrated. The residue is washed with DCM. The combined filtrates are evaporated, which afforded 10.1 g of a yellow oil, which is further purified by flash chromatography (silicagel, DCM / methanol / conc. ammonia 90:9:1). Yield: 4.02 g (66%) of a white solid. MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

(2) **Step B: 2-(4-Amino-piperidin-1-yl)-ethanol (192)**

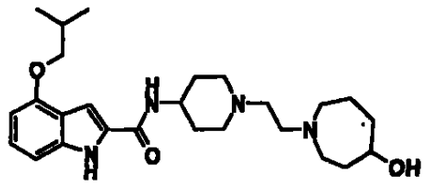
Compound 191 (4.02 g, 16.46 mmol) are treated with 4M HCl in dioxane (60 ml, 240 mmol) and the mixture is stirred at room temperature for 1 h. The white precipitate is filtered off, washed with ether and dried under high vacuum. The mother liquor is concentrated and treatred with ether. The white solid is filtered off and dried under high vacuum.
Yield: 3.42 g (95.8%). MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

(3) **Step C: 4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide (190)**

4-Isobutoxy-1H-indole-2-carboxylic acid 80 (preparation see Example 8, 1 g, 4.29 mmol) is suspensed in 5ml of DMF, cooled to 0°C and treated with HÜnig's Base (1.48 ml, 8.58 mmol). The mixture is stirred for 15 min at 0°C. In a separate reaction flask, compound 192 (931 mg, 4.29 mmol) in 10 ml of DMF is cooled to 0°C, treated with 10M aqueous sodium hydroxide solution (0.858 ml, 8.58 mmol) and stirred for 15 min at this temperature. This solution is added to the above mentioned mixture, followed by benzotriazol-1-yl-oxytripyrrolidinphosphonium hexafluorophosphate (PyBOP, 2.34 g, 4.5 mmol) and stirred for 4 h at room temperature. The reaction mixture is diluted with ethyl acetate and washed with 2N sodium hydroxide solution, water and brine. Evaporation gave a semisolid, yellow crude product, which is treated with ether, filtered of and washed with ether.
Yield: 657 mg (83%). MS (ESI): 443.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Example 151

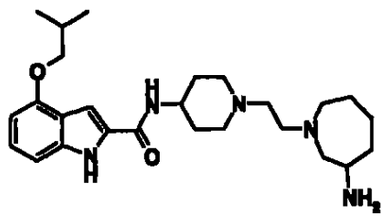
4-Isobutoxy-1H-indole-2-carboxylic acid [1-[2-(4-hydroxy-azepan-1-yl)-ethyl]-piperidin-4-yl]-amide



This compound is synthesized analogously to example 150 from 4-isobutoxy-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide, 190 and azepan-4-ol.
Yield: 36 mg (80%). MS (ESI): 457 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.19(d, 1H), 7.23 (s, 1H), 7.02 (t, 1H), 6.98 (d, 1H), 6.44 (d, 1H), 4.35 (d, 1H), 3.84 (d, 2H) 3.80-3.62 (m, 2H), 3.29 (s, 1H), 2.88 (d, 2H), 2.68-2.30 (m, 8H), , 2.14-2.06 (m, 1H), 2.0 (t, 2H), 1.83-1.34 (m, 9H), , 1.05 (d, 6H).

Example 152

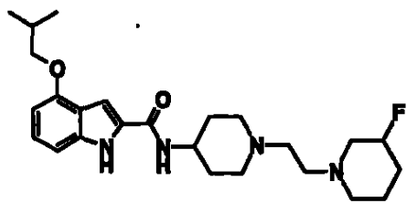
4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-amino-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized analogously to example 150 from 4-isobutoxy-1H-indole-2-carboxylic acid [1-(2-hydroxy-ethyl)-piperidin-4-yl]-amide, 190 and azepan-3-ylamine. Yield: 48 mg (36%). MS (ESI): 456.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.5(s, 1H), 8.27 (d, 1H), 7.24 (s, 1H), 7.05 (t, 1H), 6.97 (d, 1H), 6.46 (d, 1H), 3.84 (d, 2H), 3.80-3.70 (m, 1H), 2.89(m, 2H), 2.79 (m, 1H), 2.68-2.62 (m,1H), 2.60-2.52 (m,4H), 2.43-2.27 (m, 3H), 2.15-2.05 (m, 1H), 2.05-1.95 (m, 2H), 1.78-1.72 (m, 2H), 1.70-1.68 (m, 2H), 1.60-1.50 (m, 6H), 1.43-1.35 (m, 1H), 1.32-1.22 (m,1H), 1.05 (d, 6H).

Example 153

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-fluoro-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

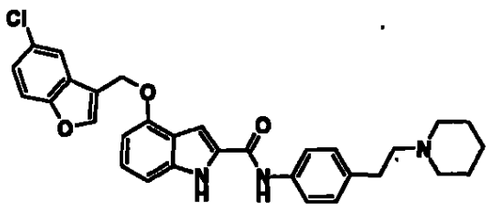


To a suspension of 190 (see example 150) (100 mg, 0.28 mmol), 3-fluoropiperidine hydrochloride (43 mg, 0.308 mmol) and DIEA (0.189 ml, 1.12 mmol) in 0.5 ml of propionitrile is added cyanomethyl-triphenyl phosphonium iodide (81 mg, 0.336 mmol). The mixture is heated at 90°C for 14 hours. The resulting solution is then diluted with EtOAc (20 ml) and washed twice with saturated sodium bicarbonate, dried over sodium sulfate and evaporated. The crude product is further purified by preparative HPLC.

Yield: 30 mg (24%). MS (ESI): 445.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 4.45-4.7 (m, 1H), 3.84 (d, 2H), 3.74 (m, 1H), 2.88 (m, 2H), 2.76 (m, 1H), 2.18-2.48 (m, 8H), 2.1 (m, 1H), 2.0 (m, 2H), 1.34-1.9 (m, 7H), 1.05 (d, 6H).

Example 154

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [4-(2-piperidin-1-yl-ethyl)-phenyl]-amide



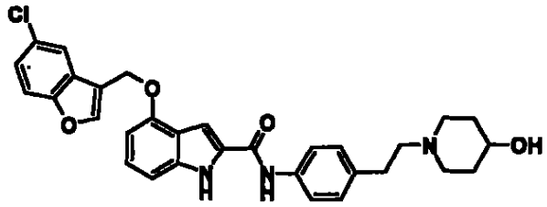
This compound is synthesized analogously to example 150 from 4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [4-(2-hydroxy-ethyl)-phenyl]-amide (193, preparation see below) and piperidine.
Yield: 140 mg (67%). MS (ESI): 528/530 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.69 (s, 1H), 10.00 (s, 1H), 8.28 (s, 1H), 7.85-7.35 (m, 6H), 7.25-7.00 (m, 4H), 6.75 (d, 1H), 5.40 (2, 2H), 2.70 (m, 4H), 2.60-2.20 (m, 4H), 1.55-1.40 (m, 6H).

Synthesis of 4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [4-(2-hydroxy-ethyl)-phenyl]-amide (193)

This compound is synthesized analogously to example 42 from 4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid (97) and 2-(4-amino-phenyl)-ethanol.
Yield: 1.59 g (69%) of a white solid. MS (ESI): 461/463 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.68 (s, 1H), 9.99 (s, 1H), 8.27 (s, 1H), 7.80 (d, 1H), 7.70-7.60 (m, 3H), 7.46 (d, 1H), 7.39 (dd, 1H), 7.20-7.10 (m, 3H), 7.06 (d, 1H), 6.75 (d, 1H), 5.37 (s, 2H) 4.59 (m, 1H), 3.57 (m, 2H), 2.67 (t, 2H).

Example 155

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {4-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-phenyl}-amide

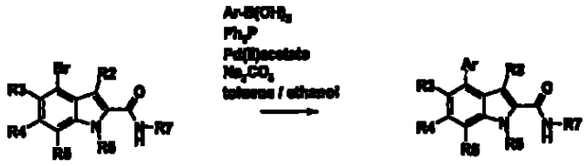


This compound is synthesized analogously to example 154 from 4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [4-(2-hydroxy-ethyl)-phenyl]-amide (193) and 2,2-dimethyl-propionic acid piperidin-4-yl ester, followed by removal of the protective group by sodium methylate.

Yield: 38 mg (34.9%). MS (ESI): 528/530 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.68 (s, 1H), 8.27 (s, 1H), 7.63 (d, 1H), 7.70-7.60 (m, 3H), 7.45 (d, 1H), 7.38 (dd, 1H) (s, 1H), 7.20-7.00 (m, 4H), 6.75 (d, 1H), 5.37 (s, 2H), 4.49 (d, 1H), 3.42 (m, 1H), 2.80-2.60 (m, 4H), 2.45-2.40 (m, 1H), 2.10-1.95 (m, 3H), 1.75-1.65 (m, 2H), 1.45-1.30 (m, 2H).

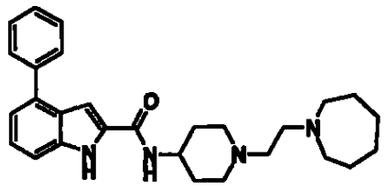
The 4-aryl-indole-2-carboxamides are generally prepared by a Suzuki coupling of the 4-bromo-indole-2-carboxamides with the corresponding aryl-boronic acids (Reaction Scheme 15).

Reaction Scheme 21:



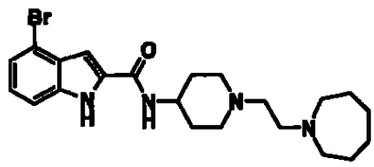
Example 156

4-Phenyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



Bromindole 194 (preparation see below) 150 mg, 0.335 mmol), Phenyl-boronic acid (82 mg, 0.67 mmol) and triphenylphosphine (26.4 mg, 0.112 mmol) are dissolved in 10 ml of toluene. After addition of 1 ml of ethanol, argon is flushed through the mixture for 30 min. Then Pd(II)acetate (3 mg, 13.4 µmol) and 2M aqueous sodiumcarbonate (0.67 ml, 1.34 mmol) are added. The mixture is stirred under reflux for 3 h. After cooling down to r.t., the mixture is treated with 30 ml of ethyl acetate and 5 % aqueous NaHCO3 solution and filtrated over celite. The organic layer is separated and evaporation under reduced pressure gave 170 mg of crude product, which is further purified by flash chromatography (silica gel, ethyl acetate / methanol conc. NH3 90:10:2) and crystallization from ethyl acetate.
Yield: 45 mg (30%) of a white solid; MS (ESI): 445.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.64 (s, 1H), 8.25 (d, 1H), 7.63 (d, 2H), 7.50 (dd, 2H), 7.40 (m, 2H), 7.31 (s, 1H), 7.23 (dd, 1H), 7.08 (d, 1H), 3.73 (m, 1H), 2.85 (m, 2H), 2.57 (m, 6H), 2.36 (m, 2H), 1.99 (m, 2H), 1.74 (m, 2H), 1.52 (m, 10H).

(1) **4-Bromo-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide (194)**

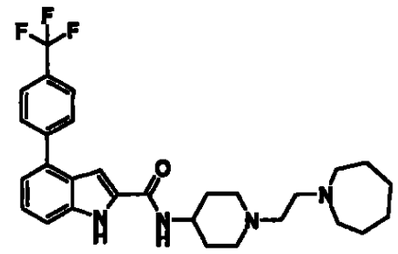


4-Bromo-1H-indole-2-carboxylic acid (1.5 g, 3.1 mmol), 1-(2-azepan-1-yl-ethyl)-piperidin-4-ylamine tri-hydrochloride (5) (2.1 g, 3.1 mmol) and DIEA (4.3 ml, 12.4 mmol) are dissolved under argon atmosphere in DMF (25 ml). TBTU (2.3 g, 3.4 mmol) is added at room temperature. The reaction mixture is stirred for 2 h at r.t., evaporated under high vacuum, dissolved in ethyl acetate and washed twice with 5% aqueous NaHCO3 solution. The organic layers are dried over sodium sulfate. Evaporation under reduced pressure gave 1.3 g (93%) of a beige solid.

MS (ESI): 447.1, 449.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.4 (d, 1H), 7.4 (d, 1H), 7.25 (d, 1H), 7.2 (s, 1H), 7.08 (dd, 1H), 3.76 (m, 1H), 2.88 (m, 2H), 2.55-2.88 (m, 6H), 2.4 (m, 2H), 2.05 (m, 2H), 1.78 (m, 2H), 1.5-1.82 (m, 10H).

Example 157

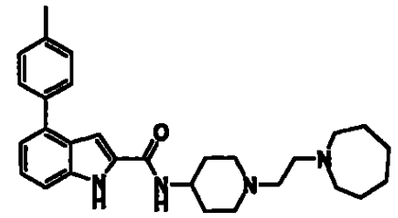
4-(4-Trifluoromethyl-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and 4-trifluoromethyl-phenyl boronic acid analogously to the method described in Example 156.
Yield: 35 mg (20%) of a white crystals; MS (ESI): 513 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.25 (d, 1H), 7.85 (s, 4H), 7.48 (d, 1H), 7.32 (s, 1H), 7.28 (dd, 1H), 7.15 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.78 (m, 2H), 1.48-1.55 (m, 10H).

Example 158

4-p-Tolyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

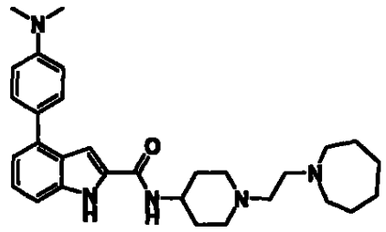


This compound is synthesized from compound 194 (see example 156) and 4-p-tolyl boronic acid analogously to the method described in Example 156.

Yield: 40 mg (28%) of a white foam; MS (ESI): 459 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.25 (d, 1H), 7.53 (d, 2H), 7.48 (d, 1H), 7.32 (d, 2H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 1H), 3.75 (m, 1H), 2.5-2.6 (m, 8H), 2.38 (s, 3H), 2.33-2.4 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48-1.55 (m, 10H).

Example 159

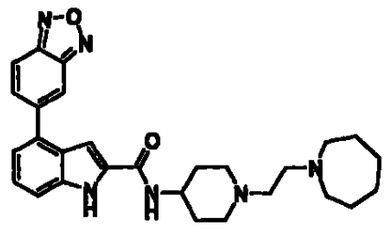
4-(4-Dimethylamino-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and (4-dimethylamino-phenyl)-boronic acid analogously to the method described in Example 156. Yield: 45 mg (28%) of a white foam; MS (ESI): 488.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 8.25 (d, 1H), 7.3-7.4 (m, 2H), 7.15-7.25 (m, 3H), 7.07 (m, 2H), 3.8 (s, 3H), 3.78 (s, 3H), 3.75 (m, 1H), 2.88 (m, 2H), 2.57 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.5 (m, 4H), 1.75 (m, 10H).

Example 160

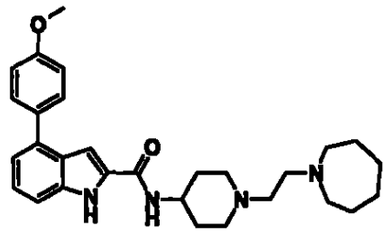
4-Benzo[1,2,5]oxadiazol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 158) and benzo[1,2,5]oxadiazol-5-yl-boronic acid analogously to the method described in Example 156.
Yield: 85 mg (39%) of a white crystals; MS (ESI): 487.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.3 (d, 1H), 8.2 (s, 1H), 8.18 (d, 1H), 7.95 (d, 1H), 7.52 (m, 1H), 7.38 (s, 1H), 7.3 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5-2.6 (m, 6H), 2.36 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 161

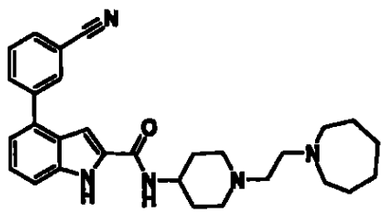
4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 158) and (4-methoxy-phenyl)-boronic acid analogously to the method described in Example 156.
Yield: 22 mg (36%) of a white foam; MS (ESI): 475.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.59 (s, 1H), 8.23 (d, 1H), 7.49 (d, 2H), 7.32 (m, 2H), 7.18 (dd, 1H), 7.0 (d, 1H), 6.85 (d, 2H), 3.75 (m, 1H), 2.97 (s, 6H), 2.67 (m, 2H), 2.56 (m, 6H), 2.48 (m, 2H), 2.0 (m, 2H), 1.77 (m, 2H), 1.52 (m, 10H).

Example 162

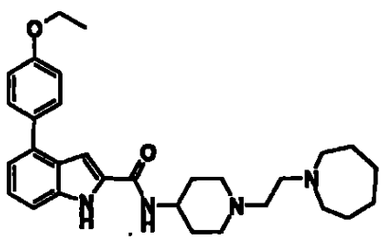
4-(3-Cyano-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and 3-cyano-phenyl boronic acid analogously to the method described in Example 156.
Yield: 115 mg (55%) of a white crystals; MS (ESI): 470.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.38 (d, 1H), 8.05 (s, 1H), 7.98 (dd, 1H), 7.88 (m, 1H), 7.72 (dd, 1H), 7.47 (d, 1H), 7.3 (d, 1H), 7.25 (d, 1H), 7.15 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48-2.6 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 163

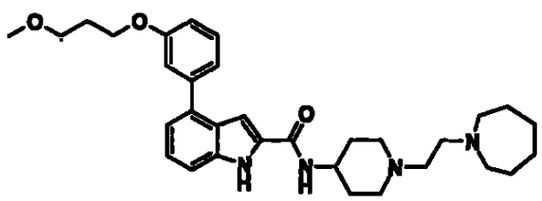
4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and (4-ethoxy-phenyl)-boronic acid analogously to the method described in Example 156.
Yield: 40 mg (24%) of beige crystals; MS (ESI): 487 $[M-H]^-$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.57 (d, 2H), 7.38 (d, 1H), 7.32 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.07 (q, 2H), 3.75 (m, 1H), 2.85 (m, 2H), 2.50-2.58 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48-1.58 (m, 8H), 1.38 (t, 3H).

Example 164

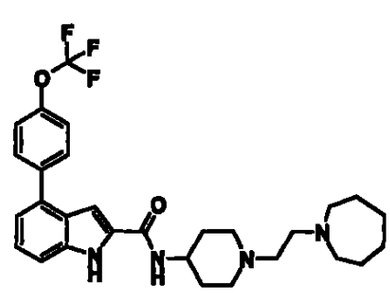
4-[3-(3-Methoxy-propoxy)-phenyl]-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and [3-(3-methoxy-propoxy)-phenyl]-boronic acid analogously to the method described in Example 156.
Yield: 180 mg (67%) of beige foam; MS (ESI): 533.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.28 (d, 1H), 7.38-7.43 (m, 2H), 7.32 (s, 1H), 7.2-7.25 (m, 2H), 7.15 (m, 1H), 7.08 (d, 1H), 6.95 (dd, 1H), 4.1 (t, 2H), 3.75 (m, 1H), 3.48 (t, 2H), 3.25 (s, 3H), 2.85 (m, 2H), 2.48-2.58 (m, 8H), 2.35 (m, 2H), 1.95-2.04 (m, 4H), 1.75 (m, 2H), 1.46-1.6 (m, 10H).

Example 165

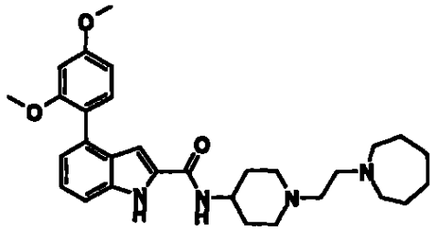
4-(4-Trifluoromethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and 4-Trifluoromethoxy-phenyl boronic acid analogously to the method described in Example 156.
Yield: 75 mg (42%) of white foam; MS (ESI): 529 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.28 (d, 1H), 7.78 (d, 2H), 7.50 (d, 2H), 7.44 (d, 1H), 7.3 (s, 1H), 7.25 (dd, 1H), 7.08 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5 - 2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.46-1.6 (m, 10H).

Example 166

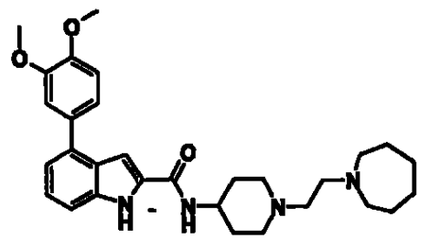
4-(2,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 166) and (2,4-dimethoxy-phenyl)-boronic acid analogously to the method described in Example 156.
Yield: 120 mg (53%) of a beige foam; MS (ESI): 505.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.15 (d, 1H), 7.34 (d, 1H), 7.2 (d, 1H), 7.15 (dd, 1H), 6.93 (d, 1H), 6.9 (d, 1H), 6.7 (d, 1H), 6.65 (dd, 1H), 3.84 (s, 3H), 3.73 (m, 1H), 3.68 (s, 3H), 2.85 (m, 2H), 2.47-2.58 (m, 8H), 2.35 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 8H).

Example 167

4-(3,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

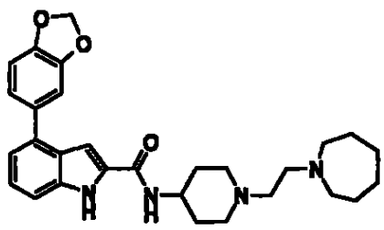


This compound is synthesized from compound 194 (see example 166) and (3,4-dimethoxy-phenyl)-boronic acid analogously to the method described in Example 156.
Yield: 65 mg (29%) of white crystals; MS (ESI): 505.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.3-7.4 (m, 2H), 7.15-7.25 (m, 3H), 7.07 (m, 2H), 3.8 (s, 3H), 3.78

(s, 3H), 3.75 (m, 1H), 2.88 (m, 2H), 2.57 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.5 (m, 4H), 1.75 (m, 10H).

Example 168

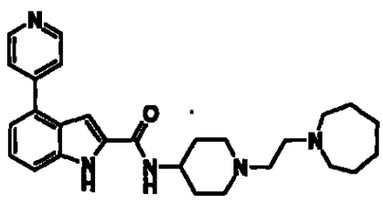
4-Benzo[1,3]dioxol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and benzo[1,3]dioxol-5-yl-boronic acid analogously to the method described in Example 156.
Yield: 75 mg (34%) of a white crystals; MS (ESI): 489.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.28 (d, 1H), 7.38 (d, 1H), 7.3 (m, 1H), 7.2 (d, 1H), 7.18 (m, 1H), 7.1 (dd, 1H), 7.04 (dd, 1H), 6.08 (s, 2H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48-2.6 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 169

4-Pyridin-4-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

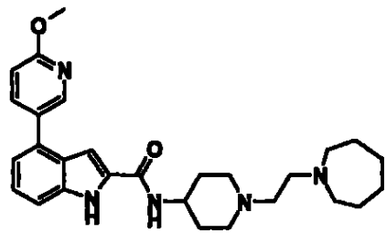


This compound is synthesized from compound 194 (see example 156) and pyridin-4-yl-boronic acid analogously to the method described in Example 156.
Yield: 35 mg (53%) of beige crystals; MS (ESI): 446.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.68 (d, 2H), 8.3 (d, 1H), 7.68 (d, 1H), 7.5 (d, 1H), 7.38 (s, 1H), 7.3 (m, 1H), 7.2

(d, 1H), 3.75 (m, 1H), 2.88 (m, 2H), 2.45-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48-1.6 (m, 10H).

Example 170

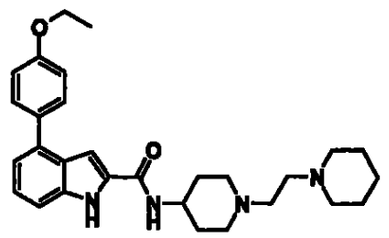
4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 194 (see example 156) and (6-methoxy-pyridin-3-yl)-boronic acid acid analogously to the method described in Example 156.
Yield: 125 mg (59%) of a white crystals; MS (ESI): 476.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.48 (d, 1H), 8.3 (d, 1H), 7.98 (dd, 1H), 7.42 (d, 1H), 7.35 (s, 1H), 7.24 (dd, 1H), 7.08 (d, 1H), 6.97 (d, 1H), 3.93 (s, 3H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48-2.6 (m, 6H), 2.35 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.58 (m, 10H).

Example 171

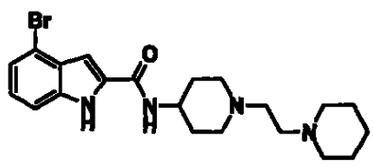
4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 195 (preparation see below) and (4-ethoxy-phenyl)-boronic acid analogously to the method described in Example 156.

Yield: 100 mg (46%) of yellow crystals; MS (ESI): 475 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.08 (q, 2H), 3.73 (m, 1H), 2.87 (m, 2H), 2.25-2.4 (m, 8H), 2.0 (m, 2H), 1.75 (m, 2H), 1.3-1.57 (m, 8H), 1.38 (t, 3H).

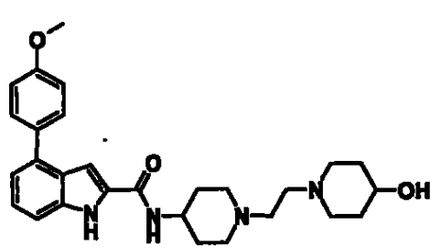
(1) 4-Bromo-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide (195)



This compound is synthesized from 4-bromo-1H-indole-2-carboxylic acid and amine 4 analogously to the method described above for the synthesis of 194 (see example 156). MS (ESI): 433, 435 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.4 (d, 1H), 7.4 (d, 1H), 7.23 (d, 1H), 7.19 (s, 1H), 7.08 (dd, 1H), 3.76 (m, 1H), 2.88 (m, 2H), 2.3-2.4 (m, 8H), 2.0 (m, 2H), 1.78 (m, 2H), 1.3-1.6 (m, 8H).

Example 172

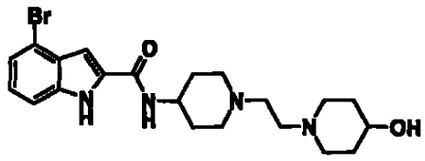
4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized from compound 196 (preparation see below) and (4-methoxy-phenyl)-boronic acid analogously to the method described in Example 156.
Yield: 55 mg (35%) of white foam; MS (ESI): 477.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.58 (d, 2H), 7.36 (d, 1H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H),

7.02 (d, 1H), 4.55 (br, 1H), 3.85 (s, 3H), 3.78 (m, 1H), 3.45 (m, 1H), 2.9 (m, 2H), 2.78 (m, 2H), 2.45 (m, 4H), 2.15 (m, 2H), 2.05 (m, 2H), 1.3 – 1.8 (m, 8H).

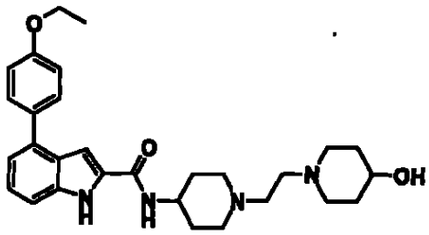
(1) **4-Bromo-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide (196)**



This compound is synthesized from 4-Bromo-1H-indole-2-carboxylic acid and amine 21 analogously to the method described for 194 (see example 166).
MS (ESI): 449, 451.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.42 (d, 1H), 7.4 (d, 1H), 7.23 (d, 1H), 7.2 (s, 1H), 7.08 (dd, 1H), 3.8 (m, 1H), 3.5 (m,1 H), 2.88 (m, 2H), 2.95 (m, 2H), 2.86 (m, 2H), 2.6 (m, 2H), 2.52 (m, 2H), 2.3 (m, 2H), 2.12 (m, 2H), 1.8 (m, 2H), 1.75 (m, 2H), 1.58 (m, 2H),1.43 (m, 2H).

Example 173

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

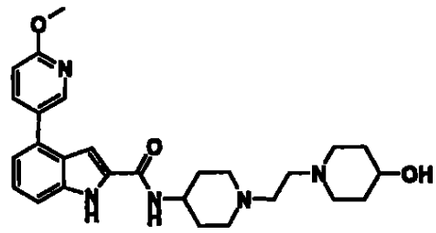


This compound is synthesized from compound 196 (see example 172) and (4-ethoxy-phenyl)-boronic acid analogously to the method described in Example 156.
Yield: 45 mg (21%) of white crystals; MS (ESI): 491 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.24 (d, 1H), 7.54 (d, 2H), 7.34 (d, 1H), 7.3 (s, 1H), 7.19 (dd, 1H), 7.06 (d, 2H), 7.0 (d, 1H), 4.47 (d, 1H), 4.08 (q, 2H), 3.73 (m, 1H), 3.40 (m, 1H), 2.85 (m, 2H), 2.68 (m,

2H), 2.36 (m, 4H), 1.98 (m, 4H), 1.74 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.37 (t, 3H), 1.32 (m, 2H).

Example 174

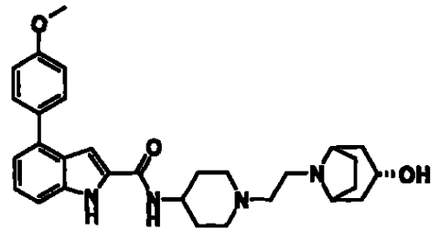
4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized from compound 198 (see example 172) and (6-methoxy-pyridin-3-yl)-boronic acid analogously to the method described in Example 156.
Yield: 28 mg (18%) of white crystals; MS (ESI): 478.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.68 (s, 1H), 8.47 (d, 1H), 8.27 (d, 1H), 7.95 (dd, 1H), 7.40 (d, 1H), 7.35 (s, 1H), 7.23 (dd, 1H), 7.09 (d, 1H), 6.97 (d, 1H), 4.48 (d, 1H), 3.92 (s, 3H), 3.75 (m, 1H), 3.39 (m, 1H), 2.85 (m, 2H), 2.68 (m, 2H), 2.36 (m, 4H), 1.99 (m, 4H), 1.75 (m, 2H), 1.65 (m, 2H), 1.54 (m, 2H), 1.35 (m, 2H).

Example 175

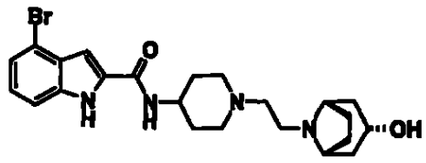
4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide



This compound is synthesized from compound 197 (preparation see below) and (4-methoxy-phenyl)-boronic acid analogously to the method described in Example 156.

Yield: 90 mg (57%) of white foam; MS (ESI): 503.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.3 (m, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.25 (br s, 1H), 3.82 (s, 3H), 3.78 (m, 1H), 3.75 (m, 1H), 3.1 (m, 2H), 2.88 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.85 (m, 2H), 1.77 (m, 4H), 1.55(m, 4H).

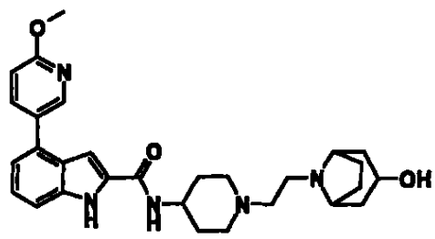
(1) **4-Bromo-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide (197)**



This compound is synthesized from 4-Bromo-1H-indole-2-carboxylic acid and amine 24 analogously to the method described for 194 (see example 156).
MS (ESI): 475.3, 477 $[M+H]^+$, 1H-NMR (DMSO-d_6, 150°C): δ (ppm) 11.7 (br s, 1H), 8.28 (br s, 1H), 7.49 (d, 1H), 7.25 (d, 1H), 7.15 (s, 1H), 7.1 (dd, 1H), 4.1 (br s, 1H), 3.97 (m, 3H), 3.5 (m,2 H), 3.0 (m, 2H), 2.5 (m, 6H), 1.9 – 2.2 (m, 10H).

Example 176

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

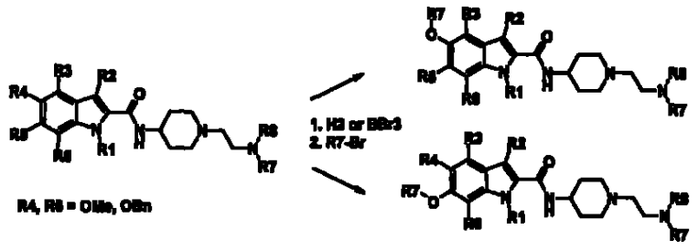


This compound is synthesized from compound 197 (see example 175) and (6-methoxy-pyridin-3-yl)-boronic acid analogously to the method described in Example 156.
Yield: 90 mg (57%) of white foam; MS (ESI): 504.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.48 (d, 1H), 8.26 (d, 1H), 7.97 (dd, 1H), 7.4 (d, 1H), 7.35 (m, 1H), 7.23 (dd,

1H), 7.08 (d, 1H), 6.95 (d, 1H), 4.23 (br, 1H), 3.93 (s, 3H), 3.78 (m, 1H), 3.75 (m, 1H), 3.1 (m, 2H), 2.88 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.8 (m, 6H), 1.53 (m, 4H).

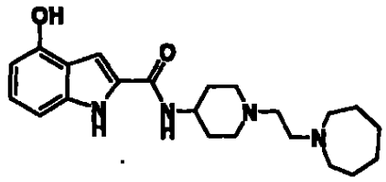
Alternatively, the 4-alkoxy-indole-2-carboxamides are prepared as shown in reaction scheme 22.

Reaction Scheme 22:



Example 177

4-Hydroxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

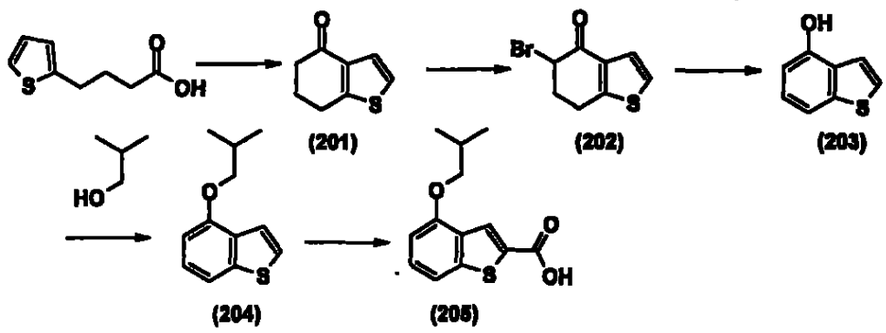


The methoxy derivative from example 1 (100 mg, 0.25 mmol) is dissolved in 5 ml of DCM. A solution of BBr3 (1M in DCM, 2.5 ml, 2.5 mmol) is added and the mixture is stirred for 18 hours. It is then poured onto ice and washed with EtOAc (30 ml). The pH of the water layer is adjusted to 9 and extracted twice with EtOAc. The organic layers are combined washed with brine, dried over anhydrous sodium sulfate and evaporated.
Yield: 24 mg (25%).
MS (ESI): 385.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 9.62 (s, 1H), 8.14 (d, 1H), 7.2 (d, 1H), 6.94 (t, 1H), 6.86 (d, 1H), 6.37 (d, 1H), 3.75 (m, 1H), 2.89 (m, 2H), 2.53-2.65 (m, 6H), 2.39 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.47-1.68 (m, 10H), 1.25 (m, 1H).

Synthesis of the benzthiophene-2-carboxamides

The 4-alkoxy-benzthiophene-2-carboxylates are synthesized starting from 4-thiophen-2-yl-butyric acid (reaction scheme 23).

Reaction Scheme 2312:



(1) 6,7-Dihydro-5H-benzo[b]thiophen-4-one (198)

Ortho-phosphoric acid (85%, 0.27 ml, 3.7 mmol) is dissolved in acetic acid anhydride (13 ml) and after addition of 4-thiophen-2-yl-butyric acid (9 g, 52.9 mmol) the mixture is stirred at 120°C for 2.5 h. The brown solution is cooled down using an ice bath, water is added and the reaction mixture is extracted with dichloromethane. The organic layers are washed with 2M NaOH solution and twice with water until a neutral pH is reached. The solution is dried over Na2SO4 and evaporated under reduced pressure. The crude product is obtained as a brown oil (7.84 g), which is further purified by flash-chromatography (silica gel, ethyl acetate / hexane 9:1).

Yield: 5.83 g (72%) of a slightly yellow solid. MS (ESI): 152 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.38 (d, 1H), 7.25 (d, 1H), 3.03 (t, 2H), 2.48 (m, 2H), 2.12 (t, 2H).

(2) 5-Bromo-6,7-dihydro-5H-benzo[b]thiophen-4-one (199)

6,7-Dihydro-5H-benzo[b]thiophen-4-one (198, 5.8 g, 38.3 mmol) is dissolved in 200 ml of dry diethyl ether and cooled down to -10°C. A solution of bromine (6.1 g, 38.3 mmol) in 30 ml of

tetrachloromethane and 2-3 drops of diethyl ether is slowly added. The mixture is stirred for 15min at -10°C, 15min at 0°C and 18h at room temperature. Then water and diethyl ether is added slowly. The organic layers are washed with water, dried over Na2SO4 and evaporated.
Yield: 8.7 g of a yellow solid (containing 23% of starting material). MS (ESI): 230, 232 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.46 (d, 1H), 7.3 (d, 1H), 4.87 (dt, 1H), 3.1 (m, 2H), 2.45 (m, 2H).

(3) Benzo[b]thiophen-4-ol (200)

5-Bromo-6,7-dihydro-5H-benzo[b]thiophen-4-one (199, 77% pure, 8.7g, 28.9 mmol), LiBr (5.7 g, 65.1 mmol) and Li2CO3 (4.3 g, 57.8 mmol) are placed under argon in 300 ml of DMF and refluxed for 3 h. The reaction mixture is allowed to cool down to room temperature and evaporated under high vacuum. After addition of ice water and cold 2M aqueous HCl solution the mixture is extracted with diethyl ether. The organic layers are extracted with 2M NaOH and the combined aqueous layers are acidified with concentrated HCl. The product is extracted twice with ethyl acetate and the organic layers are washed with saturated NaCl solution, dried over Na2SO4 and evaporated under reduced pressure.
Yield: 4.7 g of a brown solid, which is used without further purification. MS (ESI): 149.0 [M-H]⁻, 1H-NMR (DMSO-d_6): δ (ppm) 9.95 (br s, 1H), 7.55 (d, 1H), 7.45 (d, 1H), 7.38 (d, 1H), 7.15 (dd, 1H), 6.72 (d, 1H).

(4) 4-Isobutoxy-benzo[b]thiophene (201)

Benzo[b]thiophen-4-ol (200, 4.3 g, 28.9 mmol) and iso-butanol (3.2 ml, 34.7 mmol) are dissolved under argon in 150 ml of toluene. After addition of triphenylphosphine (9.1 g, 34.7 mmol) and a 40% solution of DEAD in toluene (16.8 ml, 34.7 mmol), the mixture is stirred at 120°C over night. After cooling down, the reaction mixture is subsequently washed with saturated aqueous NaHCO3 solution and NaCl solution, dried over Na2SO4 and evaporated under reduced pressure. Triphenylphosphinoxid is removed by crystallization from ethyl acetate and hexane and the crude product is further purified by flash chromatography (silica gel, hexane / ethyl acetate 9:1).
Yield: 5.4 g (91%) of a yellow oil. MS (ESI): 206 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 7.62 (d, 1H), 7.5 (d, 1H), 7.44 (d, 1H), 7.27 (dd, 1H), 6.85 (d, 1H), 3.88 (d, 2H), 2.12 (m, 1H), 1.05 (d, 6H).

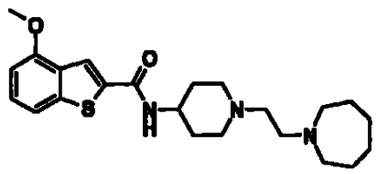
(5) 4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid (202)

A 1.6 M solution of n-butyl lithium in hexane (18 ml, 28.8 mmol) is dissolved under an argon atmosphere in 100 ml of dry diethyl ether, followed by dropwise addition of a solution of 4-isobutoxy-benzo[b]thiophene (201, 5.4 g, 26.1 mmol) in 40 ml of diethyl ether. The reaction mixture is refluxed for 45 min, then cooled down and transferred via syringe to a mixture of excess dry ice (115g, 2.61 mol) in diethyl ether (the dry ice is washed before twice with diethyl ether). The mixture is allowed to stir overnight at room temperature, then distributed between diethyl ether and water. The ether layers are reextracted with water. The aqueous layers are acidified with 2M aqueous HCl solution, and the precipitate is filtered off, washed with water and dried under high vacuum.

Yield: 3.72 g (57%) of a white solid. MS (ESI): 250 [M]+, 1H-NMR (DMSO-d_6): δ (ppm) 13.4 (br s, 1H), 7.98 (s, 1H), 7.55 (d, 1H), 7.43 (dd, 1H), 6.9 (d, 1H), 3.9 (d, 2H), 2.14 (m, 1H), 1.05 (d, 6H).

Example 178

4-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



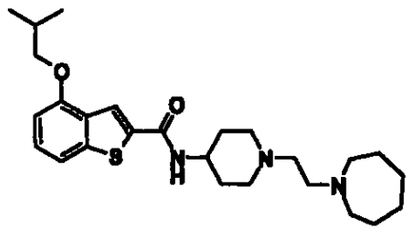
A solution of a mixture of 4- and 6-methoxy-benzo[b]thiophene-2-carboxylic acid (*C. R. Hebd. Seances Acad. Sci.* **1965**, *261*, 705) (440 mg, 1.05 mmol), amine 5 (357 mg, 1.05l) in 10 ml of DMF is treated with EDC (178 mg, 1.05 mmol), HOBT hydrate (178 mg, 1.15 mmol) and triethylamine (0.44 ml, 3.15 mmol) . The mixture is stirred over night and then evaporated under high vacuum. The crude residue is dissolved in ethyl acetate and washed twice with sodium bicarbonate (10%), brine and dried over sodium sulfate. The crude product is then purified by flash chromatography (ethyl acetate / methanol / ammonia 90:10:1).

Yield: 45 mg (10%) of a yellow solid (and 84 mg of the 6-substituted isomer). MS (ESI): 416.1 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.53 (d, 1H), 8.2 (s, 1H), 7.5 (d, 1H), 7.37 (dd,

1H), 6.9 (d, 1H), 3.94 (s, 3H), 3.7 (br m, 1H), 2.88 (m, 2H), 2.6 (m, 6H), 2.4 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.6 (m, 10H).

Example 179

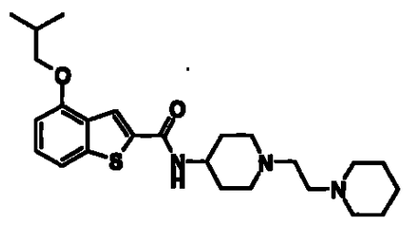
4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized from compound 202 and amine 5 analogously to the method described in Example 178.
Yield: 340 mg (53%) of beige powder. MS (ESI): 458.4 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.58 (d, 1H), 8.15 (s, 1H), 7.5 (d, 1H), 7.35 (dd, 1H), 6.88 (d, 1H), 3.9 (d, 2H), 3.7 (br m, 1H), 2.9 (m, 2H), 2.6 (m, 6H), 2.4 (m, 2H), 2.15 (m, 1H), 2.0 (m, 2H), 1.78 (m, 2H), 1.5-1.65 (m, 10H), 1.05 (d, 6H).

Example 180

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide



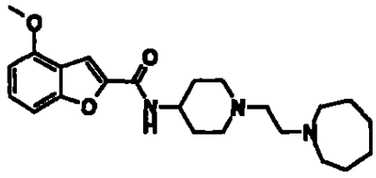
This compound is synthesized from compound 202 and amine 1 analogously to the method described in Example 178.

Yield: 93 mg (26%) of beige powder. MS (ESI): 444.3 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.58 (d, 1H), 8.15 (s, 1H), 7.48 (d, 1H), 7.35 (dd, 1H), 6.88 (d, 1H), 3.9 (d, 2H), 3.7 (br m, 1H), 2.88 (m, 2H), 2.3 – 2.4 (m, 8H), 2.15 (m, 1H), 1.98 (m, 2H), 1.78 (m, 2H), 1.58 (m, 2H), 1.47 (m, 4H), 1.35 (m, 2H), 1.05 (d, 6H).

Synthesis of the benzofuran-2-carboxamides

Example 181

4-Methoxy-benzofuran-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide



This compound is synthesized analogously to Example 1 from 4-Methoxy-benzofuran-2-carboxylic acid and amine 5.
MS (ESI): 400.2 $[M+H]^+$, 1H-NMR (DMSO-d_6): δ (ppm) 8.42 (d, 1H), 7.5 (s, 1H), 7.37 (t, 1H), 7.21 (d, 1H), 6.84 (d, 1H), 3.92 (s, 3H), 3.72 (m, 1H), 2.88 (m, 2H), 2.35-2.68 (m, 8H), 2.02 (m, 2H), 1.76 (m, 2H), 1.48-1.67 (m, 10H).

The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g.as CCR2 and CCR5 antagonists as indicated in in vitro tests as described below.

a) CCR2 membrane binding assay

The SPA (Scintillation Proximity Assay) technology is used to show that the test compounds prevent MCP-1 from binding to cell membranes expressing the CCR2 receptor. Transfected CHO-dukX cells stably expressing the hCCR2b gene are grown in MEM alpha medium to a confluency of between 70 and 80 %. After discarding the medium, 30 ml ice-cold physiological buffer solution containing 1 mM EDTA are added and the cells removed from the plate using a scraper. The cell suspension is centrifuged at 800 g for 10' at 4 °C and the cell pellet resuspended in buffer. Cell lysis is done using a Polytron PT3300D instrument at

28 000 RPM for 2 times 30 seconds on ice. Membranes are collected by centrifugation at 42 000 g for 20 minutes at 4 °C and subjected to a second round of lysis (Polytron, 28 000 RPM, 2x30 seconds on ice). Following centrifugation at 42 000 g for 20 minutes at 4 °C the membranes are resuspended in buffer at a protein concentration of 2 mg/ml and stored at -80 °C. Ten millimolar stock solutions of test compounds in 100% DMSO are prepared. Test compounds are further diluted in buffer to yield the four-fold concentrated solutions for the tests that assayed a range of 10^{-10} to 10^{-5} M. The SPA assay is performed in a final volume of 200 µl per well in 96 well plates. The components are added per well in the following order:

50 µl	Buffer (+/- test compound)
50 µl	Wheat germ agglutinin-SPA beads (1.25 mg/well) in buffer
50 µl	CCR2B membrane suspension diluted with buffer to 0.04 mg/ml (2 µg/well), alternatively 50'000 cells per well
50 µl	[^{125}I] MCP-1 in buffer (60 pM final concentration, 2.5 µCi/plate)

After addition of all components the plate is sealed and incubated for 90 minutes at room temperature with constant shaking. Following incubation the plate is centrifuged at 1000 RPM in a Sorvall RC3B centrifuge for 4 minutes at room temperature and counted for 3 minutes per well in a TOP COUNT instrument (Packard). The quench-corrected counts are used for the analysis of radioligand binding.
Compounds of formula I have an IC_{50} between 0.0003 and 10 µM.

In a similar manner, binding assays for the rat, mouse and rhesus monkey CCR2 receptors have been established. Due to the species specificity of the CCR2 antagonists, the compounds of formula I have an IC_{50} between 0.015 and 10 µM on mouse CCR2 and between 0.020 and 10 µM on rat CCR2.

<u>b) CCR2 functional assay – Ca2+ mobilization</u>

hCCR2b-CHO#84 cells:

CHOdukX cell line stably expressing the hCCR2 gene is grown in MEMα up to a confluence of 80%. The day before the experiment, cells are harvested from the tissue culture flask by trypsinization, washed, plated in a black/clear bottom 96-well plate at $5x10^4$ cells per well and cultured overnight at 37°C in a humid atmosphere enriched with 5% CO_2. On the next

day, cells are washed twice and loaded for 1 hour at RT in the dark with 2 µM Fluo-4 in buffer C. After two further washes, the cells are resuspended in buffer D. Serial dilutions of the compounds, in buffer D, are mixed with the cells and incubated for half an hour at RT in the dark. Cells are then stimulated by the injection of MCP-1 and calcium fluxes are monitored using the Flexstation™, a benchtop scanning fluorometer with and integrated fluid transfer workstation.

	HBBS* 1X	20mM Hepes	0.1% BSA	625µM Probenecid	0.5% BSA
Buffer A	X	X			
Buffer B	X	X	X		
Buffer C	X	X		X	
Buffer D	X	X		X	X

* Hank's balanced alt Solution (10X) without phenol red (#14065-049, Gibco BRL).

hCCR2b-300.19 cells:

Pre-B cell line 300-19 stably expressing the hCCR2 gene (Loetscher et al., J. Biol. Chem. 276 (5), 2986-91 (2001)) is grown in RPMI 1640 with glutamax-I supplemented with 1X MEM non essential amino-acid, 1 mM sodium pyruvate, $5x10^{-5}$ M β-mercaptoethanol and 10 % FCS. For the experiment, the cells are used in the exponential growing phase, at a maximal concentration of $1.5x10^6$ cells per ml. Cells are washed in buffer A and loaded at about 2.10^6 cells per ml in 2 µM fluo-4 in buffer B for 30 min. in the dark, at 37°C in a waterbath. After two washes with buffer A, cells are plated in black/clear bottom 96-well plate at $2x10^5$ cells per well in buffer B. All following steps, including the compound and the chemokine dilutions, are performed as described above for the hCCR2b-CHO#84 cells, except that buffer B is used instead of buffer D.

In this assay, compounds of formula I have an IC_{50} between 0.0005 and 10 µM.

c) CCR2 functional assay – chemotaxis

An *in vitro* cell migration assay for CCR2-dependent chemotaxis based on Transwell™ membrane inserts is used to profile the compounds. The assay is performed with the human monocytic THP-1 cell line and activated peripheral blood lymphocytes (PBL). THP-1 cells are cultured in RPMI1640 supplemented with 10 % heat-inactivated FCS. Activated PBL are prepared from human blood by elutriation and then activated by culture on anti-human CD3-coated culture plates and expanded by subsequent culture in medium supplemented with IL-2. Aliquots of activated PBL are frozen in liquid nitrogen and used in migration experiments

after thawing and overnight culture. Cells from cultures at a density of less than 1.2 x 10⁸ cells/ml are counted, washed and resuspended at an appropriate density in RPMI1640 containing 0.5 % BSA. Transwell™ membrane inserts of 6.5 mm diameter, 3 or 8 µm pore size and tissue culture treated polycarbonate membrane are used for the migration assays. The transwell inserts are loaded with cells and compounds in a final volume of 100 µl in RPMI1640/0.5 % BSA. For THP-1 cells, 8 µm pore size inserts are used. For PBLs the use of 3 µm pore size inserts resulted in lower non-specific counts. The inserts are placed in a 24-well tissue culture plate containing recombinant human MCP-1 and compounds in a final volume of 600 µl. After allowing the cells to migrate to the bottom compartment, the assay is stopped by removing and discarding the transwell inserts. Cells in the bottom compartment are collected and counted on a FACScan flow cytometer by acquiring all events for 30 s with settings established for each cell type. Migration is expressed as absolute cell counts/30 s relative to the input cell number measured under the same conditions.

In this assay, compounds of formula I have an IC_{50} between 0.0012 and 10 µM.

d) CCR5 membrane binding assay

Human CCR5 is used to generate stable transfectants in CHO K1 cells. Membranes prepared from these CCR5 transfectants are used in a radioligand binding assay using 125-I-MIP-1α as a ligand and the compounds of formula I are tested for inhibitory activity. The data are reported as IC_{50}, i.e. the concentration of compound required to achieve 50% inhibition of [I-125]MIP-1α binding. In this assay, compounds of formula I have an IC_{50} between 0.004 and 10 µM.

The Agents of the invention are effective as dual CCR-2 and CCR-5 antagonists. Thus the Agents of the invention are useful for the prophylaxis and treatment of CCR-2 and CCR-5 mediated diseases or medical conditions. CCR-2 and CCR-5 play an important role in leukocyte trafficking, in particular in monocyte migration to inflammatory sites and thus the agents of the invention may be used to inhibit monocyte migration e.g. in the treatment of inflammatory conditions, allergies and allergic conditions, autoimmune diseases, chronic pain, graft rejection, cancers which involve leukocyte filtration, stenosis or restenosis, atherosclerosis, rheumatoid arthritis, osteoarthritis and chronic pain.

Diseases or conditions which may be treated with the Agents of the Invention include:
Inflammatory or allergic conditions, including respiratory allergic diseases such as asthma, allergic rhinitis, COPD, hypersensitivity lung diseases, hypersensitivity pneumonitis, interstitial lung disease (ILD), (e.g. idiopathic pulmonary fibrosis, or ILD associated with autoimmune diseases such as RA, SLE, etc.); chronic obstructive pulmonary disease, anaphylaxis or hypersensitivity responses, drug allergies (e.g. to penicillins or cephalosporins), and insect sting allergies; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies, scleroderma; psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis;
Autoimmune diseases, in particular autoimmune diseases with an aetiology including an inflammatory component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente, psoriatic arthritis and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies. Specific auto-immune diseases for which Antibodies of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and irritable Bowel Syndrome), autoimmune thyroiditis, Behcet's disease, endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy);
graft rejection (e.g. in transplantation including heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, or corneal transplants) including allograft rejection or xenograft rejection or graft-versus-host disease, and organ transplant associated arteriosclerosis; atheroeclerosis;
cancer with leukocyte infiltration of the skin or organs; breast cancer;

stenosis or restenosis of the vasculature, particularly of the arteries, e.g. the coronary artery, including stenosis or restenosis which results from vascular intervention, as well as neointimal hyperplasia;
stroke;
and other diseases or conditions involving inflammatory responses including reperfusion injury, hematologic malignancies, cytokine induced toxicity (e.g. septic shock or endotoxic shock), polymyositis, dermatomyositis, and granulomatous diseases including sarcoidosis; infectious diseases, including HIV and AIDS.

The term "treatment" as used herein is to be understood as including both therapeutic and prophylactic modes of therapy e.g. in relation to the treatment of neoplasia, therapy to prevent the onset of clinically or preclinically evident neoplasia, or for the prevention of initiation of malignant cells or to arrest or reverse the progression of premalignant to malignant cells, as well as the prevention or inhibition of neoplasia growth or metastasis. In this context, the present invention is, in particular, to be understood as embracing the use of compounds of the present invention to inhibit or prevent development of skin cancer, e.g. squamus or basal cell carcinoma consequential to UV light exposure, e.g. resultant from chronic exposure to the sun.

Agents of the invention are particularly useful for treating diseases of bone and cartilage metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides, e.g. rheumatoid arthritis, and bone loss in general, including age-related bone loss, and in particular periodontal disease.

The Agents of the invention may also be used in ocular applications which include the treatment of ocular disorders, in particular of ocular inflammatory disorders, of ocular pain including pain associated with ocular surgery such as PRK or cataract surgery, of ocular allergy, of photophobia of various etiology, of elevated intraocular pressure (in glaucoma) by inhibiting the production of trabecular meshwork inducible glucocorticoid response (TIGR) protein, and of dry eye disease.

For the above indications, the appropriate dosage will, of course, vary depending upon, for example, the particular Agent of the invention to be employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However,

In prophylactic use, satisfactory results are generally indicated to be obtained at dosages from about 0.05 mg to about 10 mg per kilogram body weight, more usually from about 0.1 mg to about 5 mg per kilogram body weight. The frequency of dosing for prophylactic use will normally be in the range from about once per week up to about once every 3 months, more usually in the range from about once every 2 weeks up to about once every 10 weeks, e.g. once every 4 or 8 weeks. Agent of the invention is conveniently administered parenterally, intravenously, e.g. into the antecubital or other peripheral vein, intramuscularly, or subcutaneously. For example, a prophylactic treatment typically comprises administering the Agent of the Invention once per month to once every 2 to 3 months, or less frequently.

The Agents of the Invention may be administered in combination with another active agent. Suitable active agents include antimetabolites (e.g. methotrexate), anti-TNF agents (e.g. Remicade® (infliximab), Enbrel® (Etanercept), Humira® (adalumimab)), anti-IL-1 agents (e.g. prainacasan, ACZ885), nucleoside and non-nucleoside revers transcriptase inhibitors, HIV protease inhibitors, fusion inhibitors and other antiretroviral agents. The active agent or agents may be administered simultaneously, separately or sequentially with the Agent of the invention.

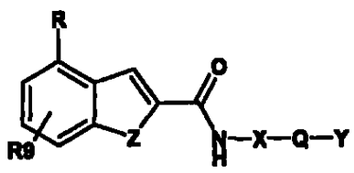
Pharmaceutical compositions of the invention may be manufactured in conventional manner. A composition according to the invention is preferably provided in lyophilized form. For immediate administration it is dissolved in a suitable aqueous carrier, for example sterile water for injection or sterile buffered physiological saline. If it is considered desirable to make up a solution of larger volume for administration by infusion rather as a bolus injection, it is advantageous to incorporate human serum albumin or the patient's own heparinised blood into the saline at the time of formulation. The presence of an excess of such physiologically inert protein prevents loss of antibody by adsorption onto the walls of the container and tubing used with the infusion solution. If albumin is used, a suitable concentration is from 0.5 to 4.5% by weight of the saline solution.

The Agents of the Invention may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Agents of the Invention may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like

preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 250mg of Agent of the invention per unit dosage.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof:



(I)

Wherein:

Z is CR_1R_2, NR_3, O or S;

R is selected from the group consisting of hydroxy, an optionally substituted C_1-C_7 alkoxy, C_2-C_7 alkenoxy, cycloalkyloxy, aryloxy, heteroaryloxy, aryl- C_1-C_7 alkoxy or heteroaryl- C_1-C_7 alkoxy, an optionally substituted C_1-C_7 alkyl or C_2-C_7 alkenyl, an optionally substituted aryl, heteroaryl or an optionally substituted aryl- C_1-C_7 alkyl group;

R9 represents one or more ring substituents selected from the group consisting of H, hydroxy, an optionally substituted C_1-C_7 alkoxy, C_2-C_7 alkenoxy, cycloalkyloxy, aryloxy, heteroaryloxy, aryl- C_1-C_7 alkoxy or heteroaryl- C_1-C_7 alkoxy, an optionally substituted C_1-C_7 alkyl or C_2-C_7 alkenyl, an optionally substituted aryl, heteroaryl or an optionally substituted aryl- C_1-C_7 alkyl group;

R_1, R_2, and R_3 are independently selected from the group consisting of H and C_1-C_7 alkyl;

X is a C_3-C_{10} cycloalkyl, heterocycloalkyl, aryl or heteroaryl each of which may be optionally substituted;

Q is a linker of between 1 and 3 atoms in length;

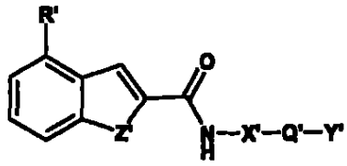
Y is C_3-C_{10} cycloalkyl, heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, aryl, heteroaryl, fused aryl-heterocycloalkyl, all of which are independently optionally substituted once or more;

the optional substituent or substituents on R and R9 being independently selected from the group consisting of halogen, hydroxy, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on X being independently selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on Y being independently selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl.

2. A compound of formula (II), or a pharmaceutically acceptable salt, ester or prodrug thereof:



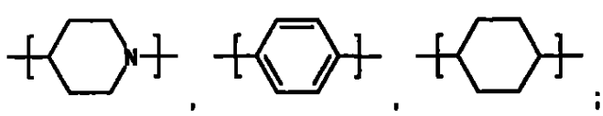
(II)

wherein:

Z' is NH, NCH_3, CH_2, S or O;

R' is hydroxy, an optionally substituted C_1-C_7 alkoxy, C_2-C_7 alkenyloxy, cycloalkyl- C_1-C_7 alkyloxy, aryloxy, heteroaryloxy, heteroaryl- C_1-C_7 alkyloxy or aryl- C_1-C_7 alkyloxy, an optionally substituted aryl, heteroaryl or an optionally substituted aryl- C_1-C_7 alkyl group;

X' is selected from the group consisting of:



Q' is selected from the group consisting of: $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$, $-CH_2-CH(CH_2OH)-$ or $-CH(CH_3)-NH(CH_3)-$;

Y' is selected from the group consisting of: C_3-C_{18} cycloalkyl, heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, aryl, heteroaryl, fused aryl-heterocycloalkyl, all of which are independently optionally substituted once or more;

the optional substituent or substituents on R' being independently selected from the group consisting of halogen, hydroxy, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di-C_1-C_7 alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, C_1-C_7

alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl;

the optional substituent or substituents on Y' being independently selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl.

3. A compound according to any one of the preceding claims selected from:

4-Methoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isopropoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclopropylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(RS)-2-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((2S,6R)-2,6-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((R)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((S)-3-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-((1R,3S,5S)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [4-(2-azepan-1-yl-ethyl)-phenyl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-[[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl]-cyclohexyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-[[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl]-phenyl)-amide

4-Isobutoxy-1H-indole-2-carboxylic acid (4-[(R)-1-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl]-phenyl)-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(3-(R)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[2-((1R,3S,5S)-3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(3-Methyl-butyloxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-Cyclopentylmethoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(1,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(2,2-Dimethyl-propoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methyl-pentyloxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(3,3-Dimethyl-butoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(Furan-2-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Benzyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(5-chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3R,4R,5S)-4-hydroxy-3,5-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(7-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Difluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3R,4R,5S)-4-hydroxy-3,5-dimethyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(7-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(5-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4-Methoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4,6-dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4,6-Dimethoxy-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5,6-dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide dihydrochloride

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide dihydrochloride

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(5,6-Dimethyl-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide dihydrochloride

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(S)-2-(4-hydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Phenoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-m-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-*m*-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(3-(RS)-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Fluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,4-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(3-RS-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(3,5-Difluoro-phenoxy)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Chloro-pyridin-2-yloxy)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide dihydrochloride

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(1-methyl-piperidin-3-ylmethyl)-piperidin-4-yl]-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3R,4R)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4R,5S)-3,4-dihydroxy-5-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-Cyclobutylmethoxy-1H-indole-2-carboxylic acid {1-[(R)-3-hydroxy-2-((3S,4S)-4-ydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3R,4R)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(2-Methyl-thiazol-4-ylmethoxy)-1H-indole-2-carboxylic acid [1-(octahydro-quinolizin-1-ylmethyl)-piperidin-4-yl]-amide

4-(Benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[2-(3,4-dihydroxy-5-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Fluoro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3RS,4SR)-3,4-dihydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(S)-2-((3RS,4SR)-3,4-dihydroxy-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(9S,9aS)-1-(octahydro-pyrido[2,1-c][1,4]oxazin-9-yl)methyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {1-[(8S,8aS)-1-(hexahydro-pyrrolo[2,1-c][1,4]oxazin-8-yl)methyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[(S)-2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-((3S,4S)-4-hydroxy-3-methyl-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-p-Tolyloxy-1H-indole-2-carboxylic acid {1-[(1S,9aR)-1-(octahydro-quinolizin-1-yl)methyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1*S*-methyl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-1*R*-methyl-ethyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2*S*-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-(Furan-3-ylmethoxy)-1H-indole-2-carboxylic acid [1-(2*R*-azepan-1-yl-propyl)-piperidin-4-yl]-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3,6-dihydro-2H-pyridin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-amino-azepan-1-yl)-ethyl]-piperidin-4-yl}-amide

4-Isobutoxy-1H-indole-2-carboxylic acid {1-[2-(3-fluoro-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid [4-(2-piperidin-1-yl-ethyl)-phenyl]-amide

4-(5-Chloro-benzofuran-3-ylmethoxy)-1H-indole-2-carboxylic acid {4-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-phenyl}-amide

4-Phenyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethyl-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-p-Tolyl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Dimethylamino-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,2,5]oxadiazol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3-Cyano-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-[3-(3-Methoxy-propoxy)-phenyl]-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Trifluoromethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(2,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(3,4-Dimethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Benzo[1,3]dioxol-5-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Pyridin-4-yl-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Ethoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-piperidin-4-yl}-amide

4-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-(6-Methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid {1-[2-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-piperidin-4-yl}-amide

4-Hydroxy-1H-indole-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Methoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4-Isobutoxy-benzo[b]thiophene-2-carboxylic acid [1-(2-piperidin-1-yl-ethyl)-piperidin-4-yl]-amide

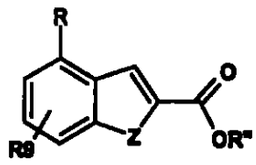
4-Methoxy-benzofuran-2-carboxylic acid [1-(2-azepan-1-yl-ethyl)-piperidin-4-yl]-amide

4. A compound according to any one of the preceding claims for use as a pharmaceutical for the prevention, amelioration or treatment of an autoimmune or inflammatory disease or condition.

5. A compound according to any one the preceding claims 1-3 for use as a pharmaceutical for the prevention, amelioration or treatment of HIV infection or AIDS.

6. A process for the preparation of a compound of formula (I) comprising:

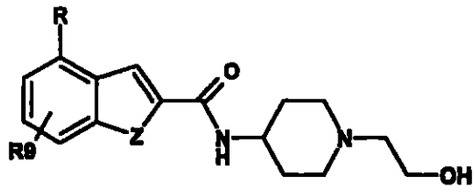
(a) reacting a compound of formula (III):



(III)

wherein R" is H or a lower alkyl group, with a compound of formula NH_2-X-Q-Y, the groups R, R9, Z, X, Q and Y being as defined in claim 1; or

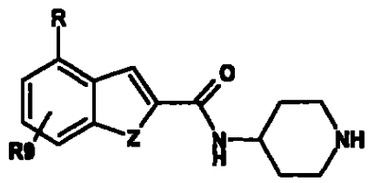
(b) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is $-CH_2-CH_2-$, and Y is a group having the formula $-NR_7R_8$ wherein N, R_7 and R_8 are linked to define collectively a heterocycloalkyl, bridged cycloalkyl, bridged heterocycloalkyl, heteroaryl, or fused aryl-heterocycloalkyl, reacting a compound of formula (IV):



(IV)

with a compound of formula NHR_7R_8, wherein R_7 and R_8 are as defined above, and R, R9 and Z are as defined earlier; or

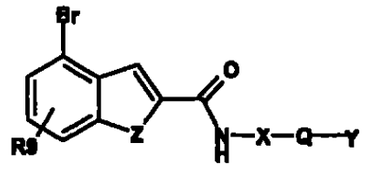
(c) for the preparation of compounds of formula (I) wherein X is piperidin-4-yl and Q is CH_2-, reacting a compound of formula (V):



(V)

in which R, R9 and Z are as defined above, with a compound of formula HO-CH_2-Y, in which Y is as defined earlier; or

(d) for the preparation of compounds of formula (I) wherein R is an optionally substituted aryl group, appropriately substituting the Br group in a compound of formula (VI) for said substituted aryl group:



(VI)

wherein Z, R9, X, Q and Y are as earlier defined;

and recovering the resultant compounds of formula (I) in free or salt form.

7. A compound obtainable by the process of claim 5.

8. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable diluent or carrier.

9. Use of a compound according to claim 1 in the manufacture of a medicament for use in the treatment of an autoimmune or inflammatory disease or condition.

10. Use of a compound according to claim 1 in the manufacture of a medicament for use in the treatment of HIV infection or AIDS.

11. A method of inhibiting chemokine receptors or macrophage protein or of reducing inflammation in a subject in need of such treatment, which method compriees administering to said subject an effective amount of a compound according to claim 1.

12. A method of treating an inflammatory or autimmune disease or condition, comprising administering to said subject an effective amount of a compound according to claim 1.

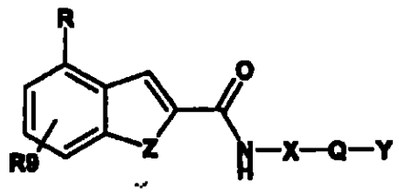
13. A method of treating HIV infection or AIDS, comprising administering to said subject an effective amount of a compound according to claim 1.

14. Use of a compound according to claim 1 in combination with one or more agents selected from: methotrexate, an anti-TNF agent, an anti-IL-1 agent, a nucleoside or non-nucleoside reverse transcriptase inhibitor, an HIV protease inhibitor, fusion inhibitor and antiretroviral agent for the treatment of an inflammatory or autimmune disease or condition or HIV or AIDS.

ANTAGONISTAS DEL RECEPTOR DE QUIMIOCINA

La invención se refiere a derivados de carbonil-amino bicíclico, los cuales son antagonistas del Receptor de Quimiocina 2 (CCR-2) y del Receptor de Quimiocina 5 (CCR-5), y a su uso en el tratamiento de enfermedades y trastornos que involucren la migración y activación de monocitos y células-T, incluyendo enfermedades inflamatorias.

De acuerdo con lo anterior, la invención, en un primer aspecto, proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o éster de profármaco del mismo:



(I)

en donde:

Z es CR_1R_2, O ó S;

R se selecciona a partir del grupo que consiste en hidroxilo, un alcoxilo de 1 a 7 átomos de carbono opcionalmente sustituido, alquenoxilo de 2 a 7 átomos de carbono, ciclo-alquiloxilo, ariloxilo, heteroariloxilo, aril-alcoxilo de 1 a 7 átomos de carbono, o heteroaril-alcoxilo de 1 a 7 átomos de carbono, un alquilo de 1 a 7 átomos de carbono, o alquenilo de 2 a 7 átomos de carbono opcionalmente sustituido, un arilo opcionalmente sustituido, heteroarilo, o un grupo

aril-alquilo de 1 a 7 átomos de carbono opcionalmente sustituido;

R9 representa uno o más sustituyentes de anillo seleccionados a partir del grupo que consiste en H, hidroxilo, un alcoxilo de 1 a 7 átomos de carbono opcionalmente sustituido, alquenoxilo de 2 a 7 átomos de carbono, cicloalquiloxilo, ariloxilo, heteroariloxilo, aril-alcoxilo de 1 a átomos de carbono o heteroaril-alcoxilo de 1 a 7 átomos de carbono, un alquilo de 1 a 7 átomos de carbono o alquenilo de 2 a 7 átomos de carbono opcionalmente sustituidos, un arilo opcionalmente sustituido, heteroarilo, o un grupo aril-alquilo de 1 a 7 átomos de carbono opcionalmente sustituido;

R_1, R_2, y R_3 se seleccionan independientemente a partir del grupo que consiste en H y alquilo de 1 a 7 átomos de carbono;

X es cicloalquilo de 3 a 18, heterocicloalquilo, arilo, o heteroarilo, cada uno de los cuales puede estar opcionalmente sustituido;

Q es un enlazador de entre 1 y 3 átomos de longitud;

Y es cicloalquilo de 3 a 18 átomos de carbono, heterocicloalquilo, cicloalquilo puenteado, heterocicloalquilo puenteado, arilo, heteroarilo, arilo-heterocicloalquilo fusionados, todos los cuales están opcionalmente sustituidos de una manera independiente una vez o más.

El sustituyente o los sustituyentes opcionales sobre R y R9 se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo inferior-amino, aminocarbonilo, mono- ó di-alquilo inferior-

248
247

aminocarbonilo, amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes, seleccionados a partir de grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo.

El sustituyente o los sustituyentes opcionales sobre X se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que

consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo.

El sustituyente o los sustituyentes opcionales sobre Y se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo.

Para evitar dudas, se debe entender que los términos enlistados en seguida, tienen los siguientes significados a través de toda la presente descripción y en las reivindicaciones:

El término "inferior", al referirse a radicales o compuestos orgánicos, significa un compuesto o radical que puede estar ramificado o no ramificado con hasta e incluyendo 7 átomos de carbono.

Un grupo alquilo inferior puede ser ramificado, no ramificado, o cíclico, y contiene de 1 a 7 átomos de carbono, de preferencia de 1 a 4 átomos de carbono. Alquilo inferior representa, por ejemplo: metilo, etilo, propilo, butilo, isopropilo, isobutilo, butilo terciario ó 2,2-dimetilpropilo.

Un grupo alcoxilo inferior puede estar ramificado o no ramificado, y contiene de 1 a 7 átomos de carbono, de preferencia de 1 a 6 átomos de carbono. Alcoxilo inferior representa por ejemplo: metoxilo, etoxilo, propoxilo, butoxilo, isopropoxilo, isobutoxilo, o butoxilo terciario. Alcoxilo inferior incluye cicloalquiloxilo y cicloalquil-alquiloxilo inferior.

Un grupo alqueno inferior, alquenilo, o alquenoxilo está ramificado o no ramificado, y contiene de 2 a 7 átomos de carbono, de preferencia de 1 a 4 átomos de carbono, y contiene cuando menos un doble enlace de carbono-carbono. Alqueno inferior, alquenilo inferior, o alqueniloxilo inferior representan, por ejemplo, vinilo, prop-1-enilo, alilo, butenilo, isopropenilo, ó isobutenilo, y sus equivalentes oxilo.

257
250

En la presente solicitud, los sustituyentes que contienen oxígeno, por ejemplo, alcoxilo, alqueniloxilo, alquiniloxilo, carbonilo, etcétera, abarcan sus homólogos que contienen azufre, por ejemplo tioalcoxilo, tioalqueniloxilo, tioalquiniloxilo, tiocarbonilo, sulfona, sulfóxido, etcétera.

Halo ó halógeno representa cloro, flúor, bromo o yodo.

Arilo representa arilo carbocíclico, arilo heterocíclico, o biarilo.

Arilo carbocíclico es un hidrocarburo cíclico aromático que contiene de 6 a 18 átomos de anillo. Puede ser monocíclico, bicíclico, o tricíclico, por ejemplo naftilo, fenilo, fenilo mono-, di-, ó tri-sustituido por uno, dos o tres sustituyentes.

Arilo heterocíclico es un hidrocarburo aromático monocíclico o bicíclico que contiene de 5 a 18 átomos del anillo, uno o más de los cuales son heteroátomos seleccionados a partir de O, N, ó S. De preferencia, hay uno o dos heteroátomos. Arilo heterocíclico representa, por ejemplo: piridilo, indolilo, quinoxalinilo, quinolinilo, isoquinolilo, benzotienilo, benzofuranilo, benzopiranilo, benzotiopiranilo, furanilo, pirrolilo, tiazolilo, oxazolilo, isoxazolilo, triazolilo, tetrazolilo, pirazolilo, imidazolilo, tienilo. Arilo heterocíclico también incluye estos radicales sustituidos.

Cicloalquilo representa un hidrocarburo cíclico que contiene de 3 a 12 átomos del anillo, de preferencia de 3 a 6 átomos del anillo. Cicloalquilo representa, por ejemplo: ciclopropilo, ciclobutilo, ciclopentilo, ó ciclohexilo. El cicloalquilo puede estar opcionalmente sustituido.

251

Heterocicloalquilo representa un hidrocarburo mono-, di-, ó tricíclico, el cual puede estar saturado o insaturado, y el cual contiene uno o más, de preferencia de 1 a 3 heteroátomos seleccionados a partir de O, N, ó S. De preferencia contiene de entre 3 y 18 átomos del anillo. El término "heterocicloalquilo" pretende también incluir los grupos cicloalquilo puenteados, tales como 3-hidroxi-8-aza-biciclo[3.2.1]oct-8-ilo.

Los ésteres de profármaco farmacéuticamente aceptables son los derivados de éster que se pueden convertir mediante solvólisis o bajo condiciones fisiológicas hasta el ácido carboxílico libre de la fórmula (I). Estos ésteres son, por ejemplo, alquilo inferior-ésteres (tales como metil- ó etil-éster), carboxi-alquilo inferior-ésteres, tales como carboximetil-éster, nitro-oxi-alquilo inferior-ésteres (tales como el 4-nitro-oxibutil-éster).

Haciendo referencia a la fórmula (I), de preferencia Z es NH, NCH_3, CH_2, S u O.

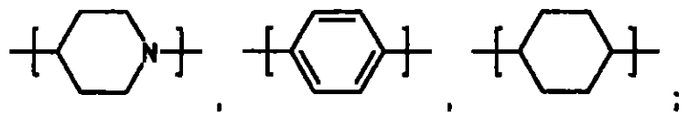
R es de preferencia hidroxilo, un alcoxilo inferior opcionalmente sustituido, alquenoxilo, cicloalquil-alquiloxilo inferior, ariloxilo, heteroariloxilo, aril-alquiloxilo inferior o heteroaril-alquiloxilo inferior, un arilo opcionalmente sustituido, heteroarilo, o un grupo aril-alquilo inferior opcionalmente sustituido.

De una manera más preferible, R es un grupo oxilo, por ejemplo alcoxilo de 1 a 7 átomos de carbono. Todavía de una manera más preferible, R es un alcoxilo de 1 a 7 átomos de carbono ramificado, o un alcoxilo de 1 a 7 átomos de carbono sustituido. Un

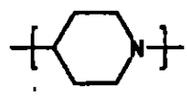
sustituyente preferido para el alcoxilo de 1 a 7 átomos de carbono sustituido es un furilo o benzofurilo que esté opcionalmente sustituido.

R9 es de preferencia hidrógeno.

X se selecciona de preferencia a partir del grupo que consiste en:



De una manera más preferible, X es:



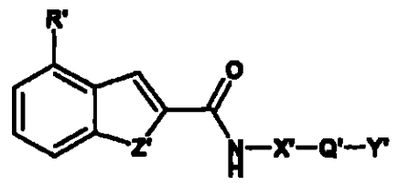
Q se define de preferencia por $-CR_4R_5$ ó $-CR_4R_5-Q_1-$, en donde Q_1 denota $-CR_6R_7-$ ó $-NR_8-$; R_4, R_5, R_6, R_7 y R_8 se seleccionan independientemente a partir del grupo que consiste en H, un alquilo inferior opcionalmente sustituido, un alquenilo inferior opcionalmente sustituido, un arilo opcionalmente sustituido, o un grupo aril-alquilo inferior opcionalmente sustituido, por ejemplo metilo, $(CH_3)_2CH-CH_2-$, $CH_3-C(=CH_2)-CH_2-$, $(CH_3)_3C-CH_2-$, bencilo;

Q se selecciona de una forma más preferible a partir del grupo que consiste en: $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH_2-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$, $-CH_2-CH(CH_2OH)-$, ó $-CH(CH_3)-NH(CH_3)-$;

Y se selecciona de preferencia a partir del grupo que consiste en: piperidinilo, azepanilo, azocanilo, fenilo, tetrahidropiranilo, 8-aza-biciclo[3.2.1]oct-8-ilo, tetrahidropiridinilo, octahidroquinolizinilo,

hexahidro-pirrolo-oxazinilo, octahidro-pirido-oxazinilo, cada uno de los cuales está opcionalmente sustituido. Los sustituyentes opcionales preferidos para Y son: hidroxilo, amino, halógeno, alquilo de 1 a 7 átomos de carbono.

Un segundo aspecto de la invención proporciona un compuesto de la fórmula (II), o una sal farmacéuticamente aceptable, éster, o profármaco del mismo:



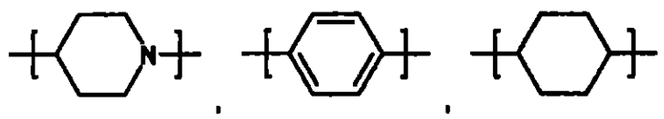
(II)

en donde:

Z' es NH, NCH_3, CH_2, S u O.

R' es hidroxilo, un alcoxilo de 1 a 7 átomos de carbono opcionalmente sustituido, cicloalquil-alquiloxilo de 1 a 7 átomos de carbono, ariloxilo, heteroariloxilo ó aril-alquiloxilo de 1 a 7 átomos de carbono, un arilo opcionalmente sustituido, heteroarilo, o un grupo aril-alquilo de 1 a 7 átomos de carbono opcionalmente sustituido;

X' se selecciona a partir del grupo que consiste en:



Q' se selecciona a partir del grupo que consiste en: $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH_2-$, -

$CH(CH_3)$-NH-, $-CH_2-N(CH_3)-$, $-CH_2-CH(CH_2OH)-$, ó $-CH(CH_3)-NH(CH_3)-$;

Y' es cicloalquilo de 3 a 18 átomos de carbono, heterocicloalquilo, cicloalquilo puenteado, heterocicloalquilo puenteado, arilo, heteroarilo, arilo-heterocicloalquilo fusionados, todos los cuales están opcionalmente sustituidos de una manera independiente una vez o más;

el sustituyente o los sustituyentes opcionales sobre R' se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo;

el sustituyente o los sustituyentes opcionales sobre Y' se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo.

Los compuestos preferidos de la fórmula (I) son:

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isopropoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isopropoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-[3S,4S)-4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(RS)-2-metil-piperidin-1-il]-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(4-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((2S,6R)-2,6-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((R)-3-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((S)-3-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((1R,3S,5S)-3-hidroxi-8-aza-biciclo[32.1]oct-8-il)-etil]-piperidin-

4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[4-(2-azepan-1-il-etil)-fenil]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

(4-{[metil-(tetrahidro-piran-4-il)-amino]-metil}-ciclohexil)-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

(4-{[metil-(tetrahidro-piran-4-il)-amino]-metil}-fenil)-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

(4-{(R)-1-[metil-(tetrahidro-piran-4-il)-amino]-etil}-fenil)-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-(3-(R)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-((1R,3S,5S)-3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[8S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3-metil-butiloxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(1,2-dimetil-propoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metil-pentiloxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,3-dimetil-butoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(furan-2-ilmetoxi)-1H-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4(furan-3-ilmetoxi)-1H-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il{-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benciloxi-1H-

indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(5-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9Ar)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-

carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida

del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3R,4R,5S)-4-hidroxi-3,5-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(7-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-ilmetil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il{-amida del ácido 4-(7-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-

carboxílico;

diclorhidrato de {1-[2-((3R,4R,5S)-4-hidroxi-3,5-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-1-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-piperidin-1-il-metil)-piperidin-4-il]-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-.benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il]-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il-propil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del

ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-fenoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico;

{1-[2-(3-(RS)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

{1-[2-(3-(RS)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3-fluoro-fenoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-

~~268~~
267

(3-fluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,4-difluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico;

{1-[2-(3-RS-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il}-amida del ácido 4-(6-cloro-piridin-2-iloxi)-1H-indol-2-carboxílico;

diclorhidrato de [1-(octahidro-quinolizin-1-ilmetil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(1-metil-piperidin-3-ilmetil)-piperidin-4-il]-amida del ácido 4-iobutoxi-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-((3R,4R)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4R,5S)-34-dihidroxi-5-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-

carboxílico;

{1-[(R)-3-hidroxi-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3R,4R)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(octahidro-quinolizin-1-ilmetil)-piperidin-4-il]-amida del ácido 4-(2-metil-tiazol-4-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(3,4-dihidroxi-5-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3RS,4SR)-3,4-dihidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(3RS,4SR)-3,4-dihidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(9S,9aS)-1-(octahidro-pirido[2,1-c][1,4]oxazin-9-il)metil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(8S,8aS)-1-(hexahidro-pirrolo[2,1-c][1,4]oxazin-8-il)metil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida

del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-1S-metil-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-1R-metil-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2S-azepan-1-il-propil)-piperidin-4-il]-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2R-azepan-1-il-propil)-piperidin-4-il]-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(3,6-dihidro-2H-piridin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-azepan-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(3-amino-azepan-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(3-fluoro-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

270

[4-(2-piperidin-1-il-etil)-fenil]-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{4-[2-(4-hidroxi-piperidin-1-il)-etil]-fenil}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1il-etil)-piperidin-4-il]-amida del ácido 4-fenil-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-trifluorometil-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-p-tolil-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-dimetilamino-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benzo[12,5]oxadiazol-5-il-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3-ciano-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-[3-(3-metoxi-propoxi)-fenil]-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-trifluorometoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(2,4-dimetoxi-

fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,4-dimetoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benzo[1,3]dioxol-5-il-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-piridin-4-il-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

{1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-hidroxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-benzo[b]tiofen-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-benzo[b]tiofen-2-carboxílico;

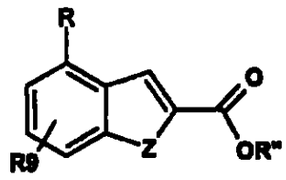
[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-benzo[b]tiofen-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-benzofuran-2-carboxílico.

De acuerdo con un tercer aspecto de la invención, se proporciona un compuesto de la fórmula (I) para utilizarse como un producto farmacéutico para la prevención, reducción o tratamiento de una enfermedad o condición autoinmune o inflamatoria.

De conformidad con un cuarto aspecto de la invención, se proporciona un proceso para la preparación de un compuesto de la fórmula (I), el cual comprende:

(a) hacer reaccionar un compuesto de la fórmula (III):



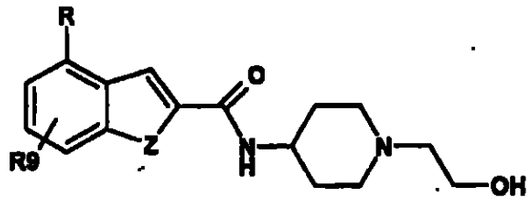
(III)

en donde R" es H o un grupo alquilo inferior, con un compuesto de la fórmula NH_2-X-Q-Y, definiéndose los grupos R, R9, Z, X, Q, e Y anteriormente; ó

(b) para la preparación de los compuestos de la fórmula (I) en donde X es piperidin-4-ilo y Q es -CH_2-CH_2-, e Y es un grupo que tiene la fórmula -NR_7R_8, en donde R_7 y R_8 están enlazados para

273

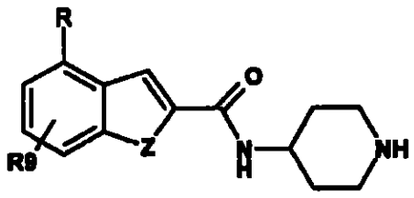
definir colectivamente un hetero-cicloalquilo, cicloalquilo puenteado, heterocicloalquilo puenteado, heteroarilo, o arilo-heterocicloalquilo fusionados, hacer reaccionar un compuesto de la fórmula (IV):



(IV)

con un compuesto de la fórmula NHR_7R_8, en donde R_7 y R_8 son como se definen anteriormente, y R, R9, y Z son como se definen anteriormente; ó

(c) para la preparación de compuestos de la fórmula (I), en donde X es piperidin-4-ilo y Q es CH_2-, hacer reaccionar un compuesto de la fórmula (V):

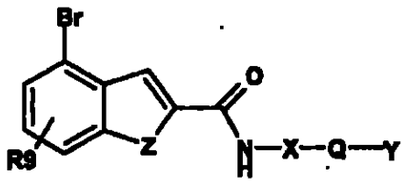


(V)

en donde R, R9 y Z son como se definen anteriormente, con un compuesto de la fórmula HO-CH_2-Y, en donde Y es como se define anteriormente; ó

(d) para la preparación de compuestos de la fórmula (I), en donde R es un grupo arilo opcionalmente sustituido, utilizar

apropiadamente el grupo Br en un compuesto de la fórmula (VI) para sustituir a este grupo arilo sustituido:



(VI)

en donde Z, R9, X, Q e Y son como se definen anteriormente;

y recuperar los compuestos resultantes de la fórmula (I) en forma libre o de sal.

El proceso de la invención se efectúa de una manera convencional.

La variante del proceso (a) es una reacción de condensación entre ácido o éster y amina. Se efectúa convenientemente mediante la reacción del ácido con la amina en la presencia de agentes de acoplamiento, por ejemplo TBTU/DIEA en un solvente tal como dimetilformamida, o mediante la reacción del éster con la amina en la presencia de un agente de acoplamiento tal como HOBT/EDC.

La variante del proceso (B) es una reacción de condensación que convenientemente se lleva a cabo utilizando un reactivo tal como yoduro de cianometil-trifenil-fosfonio y base de Hunig.

La variante del proceso (c) es una reacción de condensación que también se lleva a cabo convenientemente utilizando un reactivo, tal como yoduro de cianometil-trifenil-fosfonio y base de Hunig.

La variante del proceso (d) es una reacción de sustitución y se

275

efectúa convenientemente utilizando el ácido aril-borónico apropiado y trifenilfosfina en la presencia de acetato de plomo (II).

Los compuestos de la invención se pueden recuperar a partir de la mezcla de reacción, y se pueden purificar de una manera convencional. Los isómeros, tales como enantiómeros, se pueden obtener de una manera convencional, por ejemplo mediante cristalización fraccionaria o síntesis asimétrica a partir de los materiales de partida asimétricamente sustituidos correspondientes, por ejemplo ópticamente activos.

Los materiales de partida y los intermediarios son conocidos o se pueden preparar de acuerdo con los métodos conocidos o de una manera análoga a la descrita en los Ejemplos.

De acuerdo con un quinto aspecto de la invención, se proporciona un compuesto que se puede obtener mediante cualquiera de los procesos anteriormente mencionados.

De acuerdo con un sexto aspecto de la invención, se proporciona una composición farmacéutica que comprende un compuesto de la fórmula (I) en asociación con un diluyente o vehículo farmacéuticamente aceptable.

De acuerdo con un séptimo aspecto de la invención, se proporciona el uso de un compuesto de la fórmula (I) en la fabricación de un medicamento para utilizarse en el tratamiento de una enfermedad o condición autoinmune o inflamatoria.

De acuerdo con un octavo aspecto de la invención, se proporciona un método para inhibir los receptores de quimiocina o

las proteínas de macrófago, o para reducir la inflamación en un sujeto que necesite dicho tratamiento, cuyo método comprende administrar a este sujeto una cantidad efectiva de un compuesto de la fórmula (I).

De acuerdo con un noveno aspecto de la invención, se proporciona un método para el tratamiento de una enfermedad o condición inflamatoria o autoinmune, el cual comprende administrar a este sujeto una cantidad efectiva de un compuesto de la fórmula (I).

Los agentes de la invención se pueden preparar mediante los procesos descritos más adelante.

SECCIÓN EXPERIMENTAL

Abreviaturas:

BOC:	Terbutiloxicarbonilo
Boc2O:	Dicarbonato de di-t-butilo
DCC:	Diciclohexil-carbodi-imida
DCE:	Dicloroetano
DCM:	Diclorometano
DEAD:	Azadicarboxilato de dietilo
DIEA:	Etil-di-isopropil-amina
DMAP:	Dimetil-piridin-4-il-amina
DME:	1,2-dimetoxi-etano
DMF:	N,N-dimetil-formamida
EDC:	Clorhidrato de (3-dimetilamino-propil)-etil-carbodi-imida

Ether:	Etoxi-etano
EtOH:	Etanol
EtOAc:	Etiléster del ácido acético
HCl:	Ácido clorhídrico
HOBT:	Benzotriazol-1-ol
LAH	Hidruro de litio y aluminio
LDA:	Di-isopropilamina de litio
MeOH:	Metanol
NaOH:	Hidróxido de sodio
NMP:	1-metil-pirrolidin-2-ona
Pd/C:	Paladio sobre carbono
TBAF:	Fluoruro de tetrabutilamonio
TBME:	t-butil-metil-éter
TBDMS:	t-butil-dimetil-sililo
TBTU:	tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-tetrametiluronio
t-BuOH	2-metil-propan-2-ol
TFA:	Ácido trifluoroacético
THF:	Tetrahidrofurano

Los espectros de ^{1}H-RMN se registran en un espectrómetro de RMN Varian Gemini de 400 MHz. Los picos significativos se tabulan en el orden: multiplicidad (s, singlete; d, doblete; t, triplete; q, cuarteto; m, multiplete; br, amplio), y número de protones. Los

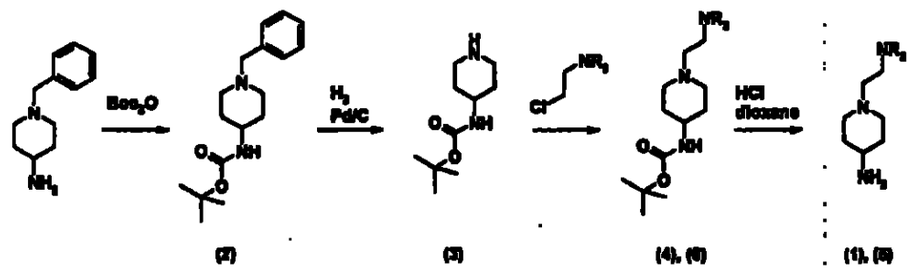
278

espectros de masas de Ionización con Pulverización de Electrones (ESI) se registran en un espectrómetro de masas Hewlett Packard 5989A. Los resultados de la espectrometría de masas se reportan como la proporción de masa sobre carga. Las purificaciones de HPLC de preparación se llevan a cabo con columnas XTerraTM RP18 de 19x150 milímetros, utilizando acetonitrilo/agua o MeOH/agua como sistemas de eluyentes. Todos los reactivos, materiales de partida, e intermediarios utilizados en estos ejemplos, están disponibles en las fuentes comerciales, o se preparan fácilmente mediante los métodos conocidos por los expertos en la materia.

Síntesis de los Bloques de Construcción de Amina

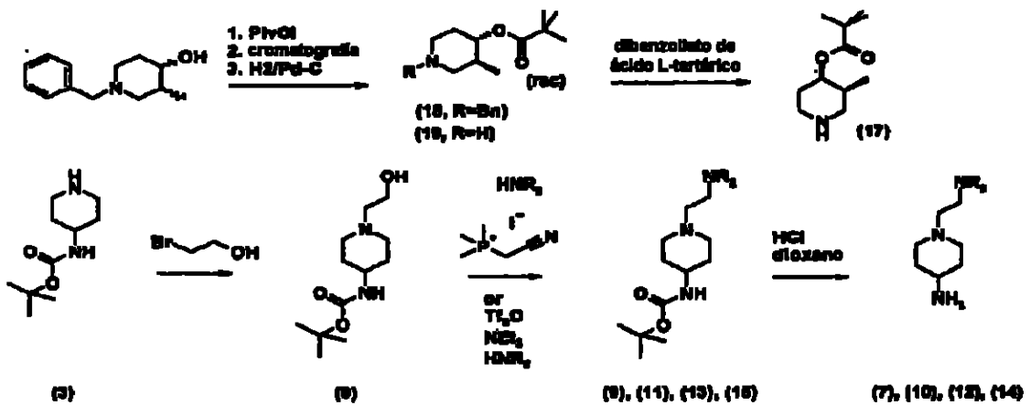
Las aminas 1, 5, 7, 10, 12, 14, 17, 20, 21, 24, 27, 30, 35, 41, 50, 56, 60, 61, 63, 67, 70 y 72 se preparan de acuerdo con los esquemas de reacción ilustrados en seguida:

Esquema de Reacción 1:

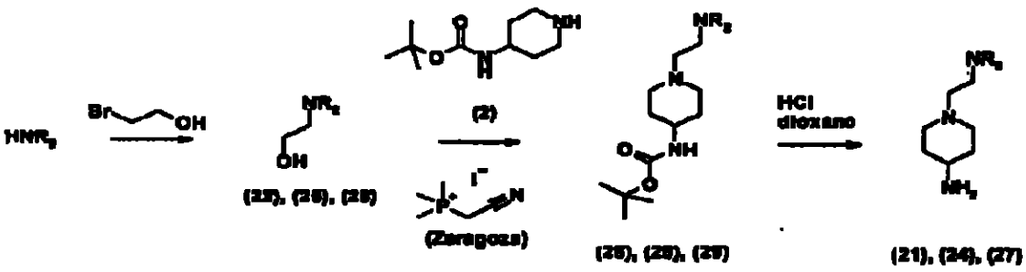


279

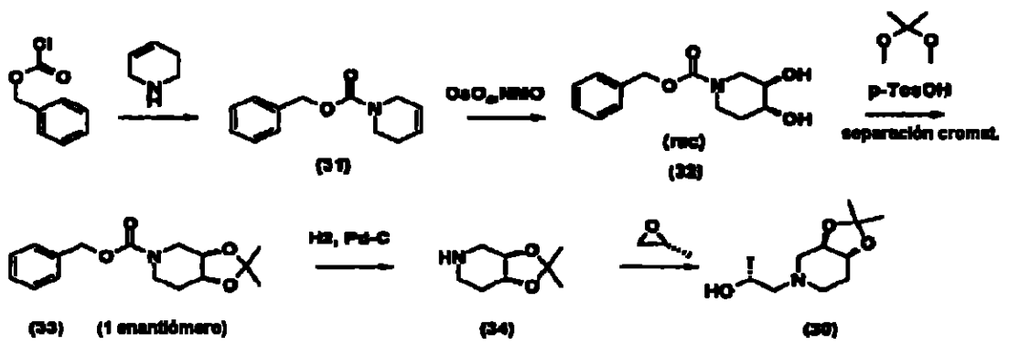
Esquema de Reacción 2:



Esquema de Reacción 3:

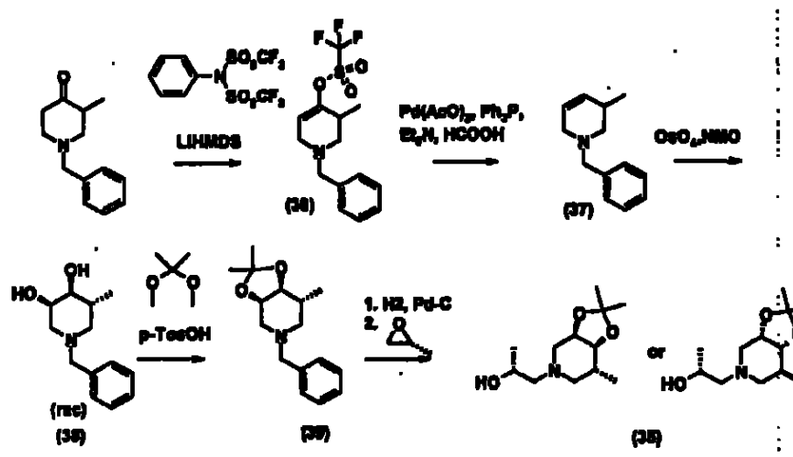


Esquema de Reacción 4:

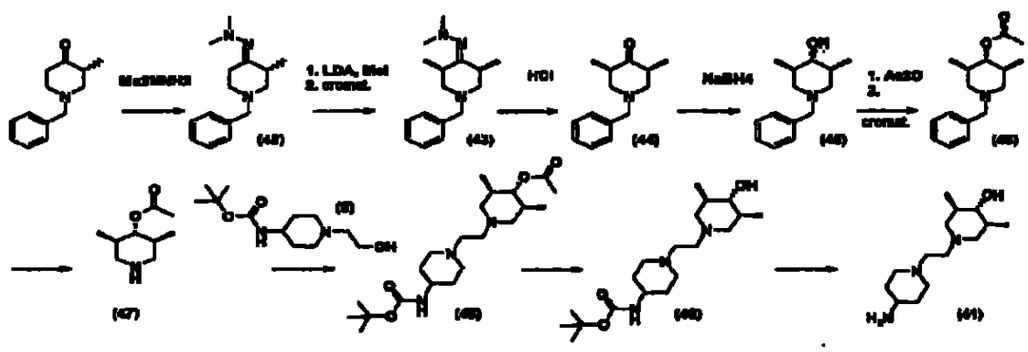


280

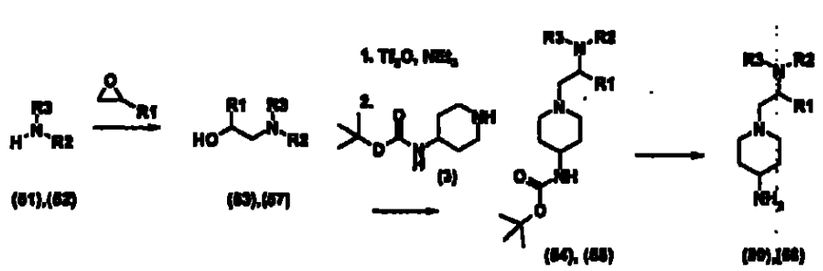
Esquema de Reacción 5:



Esquema de Reacción 6:

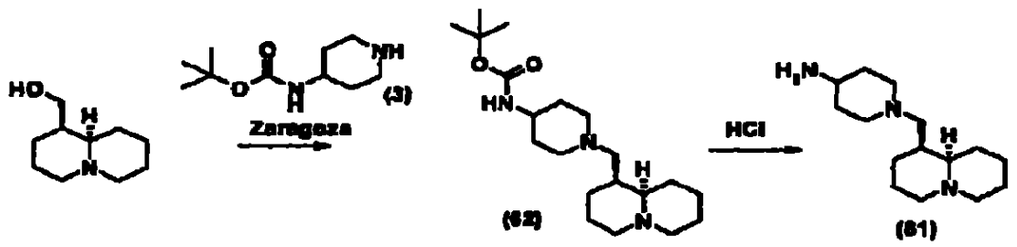


Esquema de Reacción 7:

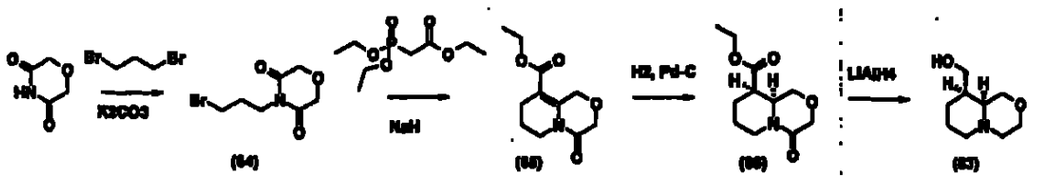


281

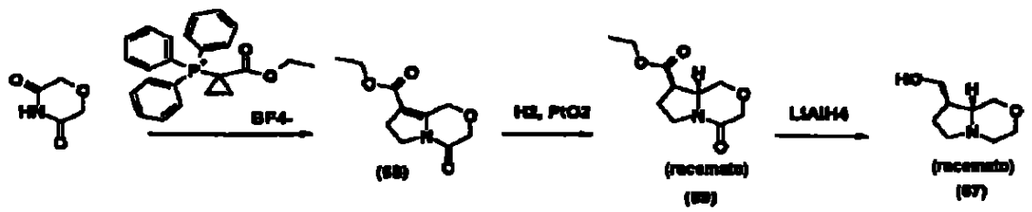
Esquema de Reacción 8:



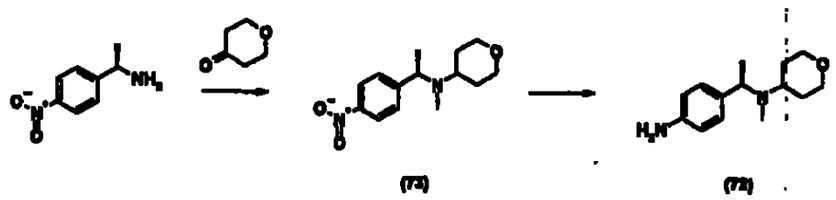
Esquema de Reacción 9:



Esquema de Reacción 10:

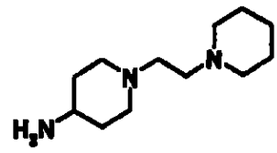


Esquema de Reacción 11:



282

Síntesis de tri-clorhidrato de 1-(2-piperidin-1-il-etil)-piperidin-4-ilamina (1) (esquema de reacción 1):



(1) Terbutil-éster del ácido (1-bencil-piperidin-4-il)-carbámico

Se disuelve 1-bencil-piperidin-4-ilamina (50 gramos, 262.76 milimoles) en una mezcla de 200 mililitros de agua, 145 mililitros de hidróxido de sodio acuoso 2 molar, y 350 mililitros de t-BuOH a 0°C. Se agrega por goteo una solución de Boc2O (63.1 gramos, 1.1 equivalentes) en 150 mililitros de t-BuOH dentro de 1 hora a 0°C. Se forma una suspensión blanca, la cual se deja agitándose durante la noche a temperatura ambiente. La mezcla de reacción se diluye con éter y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio anhidro y se evaporan bajo presión reducida.

Rendimiento: 71.5 gramos de un sólido amarillo pálido (93 por ciento). MS (ESI): 291 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.2-7.35 (m, 5H), 6.77 (br d, 1H), 3.44 (s, 2H), 3.22 (br m, 1H), 2.75 (m, 2H), 1.95 (dt, 2H), 1.68 (m, 2H), 1.38 (s, 9H), 1.36 (dt, 2H).

(2) Terbutiléster del ácido piperidin-4-il-carbámico (3)

Una solución del éster 2 anterior (66 gramos, 227.27 milimoles) en 1 litro de etanol, se hidrogena bajo presión normal con 10 gramos de Pd/C (10 por ciento) durante 16 horas a temperatura ambiente. La

283

mezcla se filtra sobre Celite, y se evapora bajo presión reducida. La recristalización a partir de éter dio 34.5 gramos (76 por ciento) de cristales blancos.

MS (ESI): 201 $[M+H]^+$, 401 [2M+H]+, 1H-RMN (DMSO-d_6): δ (ppm) 6.7 (br d, NH), 3.22 (br m, 1H), 2.88 (dt, 2H), 2.39 (dt, 2H), 1.8 (br s, NH), 1.6 (dt, 2H), 1.35 (s, 9H), 118 (dt, 2H).

(3) Terbutiléster del ácido 1-(2-piperidin-1-il-etil)-piperidin-4-il]-carbámico

Se disuelven terbutil-éster del ácido piperidin-4-il-carbámico (3) (4.8 gramos, 23.72 milimoles), clorhidrato de 1-(2-cloro-etil)-piperidina (53 gramos, 26.09 milimoles) y DIEA (8.9 mililitros, 52.18 milimoles) en 150 mililitros de cloroformo, y se ponen a reflujo durante 18 horas. Después de la adición de más clorhidrato de 1-(2-cloro-etil)-piperidina (2.65 gramos, 13.05 milimoles) y DIEA (4.4 mililitros, 26.09 milimoles), la mezcla de reacción se pone a reflujo durante otras 4 horas. Después de enfriar a temperatura ambiente, la mezcla se diluye con DCM y se lava con agua y una solución acuosa de carbonato ácido de sodio al 5 por ciento. La evaporación dio 7.3 gramos de cristales castaños, los cuales se recristalizan a partir de éter/hexano.

Rendimiento: 5.3 gramos (72 por ciento) de cristales beiges. MS (ESI): 312 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6-75 (br d, NH), 3.18 (br m, 1H), 2.8 (m, 2H), 2.23-2.4 (m, 8H), 1.92 (dt, 2H), 1.65 (m, 2H), 1.48 (m, 4H), 1.38 (s, 9H), 1.3-1.4 (m, 4H).

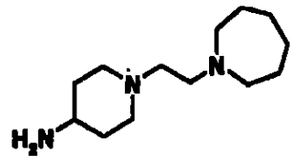
284

(4) Tricl rhidrato de 1-(2-piperidin-1-il-etil)-piperidin-4-ilamina (1)

El éster 4 anterior (5.2 gramos, 16.7 milimoles) se suspende a 0°C en 60 mililitros de una solución 4M de HCl en dioxano, y se agita a temperatura ambiente durante 3 horas. Después de a evaporación bajo presión reducida, el producto crudo se seca a un alto vacío.

Rendimiento: 5.3 gramos (99 por ciento) de cristales beiges claros. MS (ESI): 212 $[M+H]^+$, 1H-RMN (D2O): δ (ppm) 4.14 (m, 2H), 4.04 (br m, 5H), 3.8 (m, 4H), 3.65 (dt, 2H), 2.85 (d, 2H), 2.45 (m, 2H), 2.35 (m, 4H), 2.15 (m, 2H).

Síntesis de triclorhidrato de 1-(2-azepan-1-il-etil)-piperidin-4-ilamina (5) (esquema de reacción 1):



(1) Terbutiléster del ácido [1-(2-azepan-1-il-etil)-piperidin-4-il]-carbámico (6)

Se sintetiza de una manera análoga al éster 4, empezando a partir de cloruro de 2-(hexametilenimino)etilo (13.8 gramos) y el éster 3 (12.4 gramos).

Rendimiento: 14 gramos de un sólido incoloro (63 por ciento). MS (ESI): 326 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.75 (br d, NH), 3.18 (br m, 1H), 2.8 (m, 2H), 2.3-2.6 (m, 8H), 1.95 (dt, 2H), 1.65 (m, 2H), 1.55 (m, 6H), 1.38 (s, 9H), 1.3-1.4 (m, 4H).

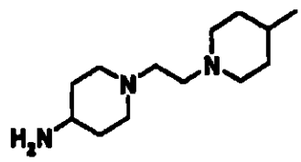
285

(2) Triclorhidrato de 1-(2-azepan-1-il-etil)-piperidin-4-ilamina

Se prepara de una manera análoga al 1, empezando a partir del éster 6 (14 gramos).

Rendimiento: 13 gramos (90 por ciento) de un sólido incoloro. MS (ESI): 226 $[M+H]^+$, 1H-RMN (120°C, DMSO-d_6): δ (ppm) 8.5 (br, NH3+), 3.5 (m, 5H), 3.4 (m, 2H), 3.3 (m, 4), 2.97 (m, 2H), 2.18 (m, 2H), 2.05 (m, 2H), 19 (m, 4H), 1. (m, 4H).

Síntesis de triclorhidrato de 1-[2-(4-metil-piperidin-1-il)-etil]-piperidin-4-ilamina (7) (esquema de reacción 2)



(1) Terbutiléster del ácido [1-(2-hidroxi-etil)-piperidin-4-il]-carbámico (8)

A una solución de terbutil-éster del ácido piperidin-4-il-carbámico 3 (10 graos, 50 milimoles) en 100 mililitros de metanol, se le agregan carbonato de sodio (21.2 gramos, 200 milimoles) y 2-bromoetanol (7.1 mililitros, 100 milimoles). La mezcla se agita durante la noche. Luego se evaporan los solventes, y el residuo se tritura con DCM, se filtra, y se evapora de nuevo. El producto crudo se purifica mediante cromatografía utilizando EtOAc/MeOH (saturado con amoniaco): 9/1.

Rendimiento: 8.07 (66 por ciento). MS (ESI): 245.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.75 (r d, 1H), 4.34 (t, 1H), 3.46 (q, 2H), 3.19 (br

286

m, 1H), 2.8 (m, 2H), 23.5 (t, 2H), 1.95 (m, 2H), 1.66 (m, 2H), 1.39 (s, 9H), 1.35 (m, 2H).

(2) Terbutiléster del ácido {1-[2-(4-metil-piperidin-1-il-}-etil]-piperidin-4-il}-carbámico (9)

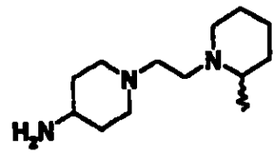
A una mezcla de éster 8 (3 gramos, 12.28 milimoles), 4-metil-piperidina (1.46 mililitros, 12.28 milimoles) y DIEA (2.7 mililitros, 15.96 milimoles) en 30 mililitros de propionitrilo, se trata con yoduro de cianometil-trimetil-fosfonio sólido (3.58 gramos, 14.74 milimoles), y se calienta a reflujo durante 3 horas. Después de enfriar a temperatura ambiente, se agrega una solución de K_2CO_3 2M hasta quedar básica, y la mezcla se extrae dos veces con DCM. Las capas orgánicas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, y se evaporan. El material crudo se purifica mediante cromatografía utilizando EtOH/MeOH (saturado con amoniaco): 9/1. Rendimiento: 2 gramos (50 por ciento). MS (ESI): 326.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.74 (br d, 1H), 3.16 (m, 1H), 2.78 (m, 4H), 2.33 (br s, 4H), 1.86 (m, 4H), 1.64 (m, 2H), 1.53 (m, 2H), 1.36 (s, 9H), 1.32 (m, 3H), 1.08 (m, 2H), 0.86 (d, 3H).

(3) Triclorhidrato de 1-[2-(4-metil-piperidin-1-il)-etil-]-piperidin-4-ilamina (7)

El terbutil-éster 9 (2 gramos, 6.14 milimoles) se suspende en 10 mililitros de dioxano. Luego se agrega DCM hasta que se disuelva el sólido. A esta mezcla, se le agrega HCl 4M en dioxano (123 mililitros, 49.2 milimoles). Después de agitar durante la noche, se evaporan los solventes para dejar un producto sólido blanco.

Rendimiento: 2.06 gramos (100 por ciento). MS (ESI): 226.2 $[M+H]^+$.

Síntesis de triclorhidrato de 1-[2-((RS)-2-metil-piperidin-1-il)-etil]-piperidin-4-ilamina (10) (esquema de reacción 2):



(1) Terbutil-éster del ácido {1-[2-((S)-2-metil-piperidin-1-il)-etil]-piperidin-4-il}-carbámico (11)

Se prepara de una manera análoga al 9, empezando a partir del terbutil-éster 8 (2 gramos, 8.19 milimoles), (S)-2-metil-piperidina (0.985 mililitros, 8.19 milimoles), DIEA (1.8 mililitros, 10.65 milimoles) y yoduro de cianometil-trimetil-fosfonio (2.39 gramos, 9.83 milimoles)

Rendimiento: 1.35 gramos (51 por ciento). MS (ESI): 326.3 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.42 (br d, 1H), 3.47 (m, 1H), 2.84 (m, 4H), 2.47 (m, 3H), 2.15-2.35 (m, 2H), 2.1 (m, 2H), 1.92 (m, 2H), 1.2-1.75 (m, 8H), 1.44 (s, 9H), 1.08 (d, 3H).

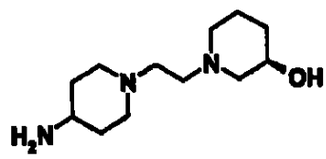
(2) Triclorhidrato de 1-[2-((RS)-2-metil-piperidin-1-il)-etil]-piperidin-4-ilamina (10)

Se prepara mediante la disociación con BOC del terbutil-éster (1.3 gramos, 3.99 milimoles) con HCl 4M en dioxano (8 mililitros, 32 milimoles), como se describe para la amina 7.

Rendimiento: 1.3 gramos (97 por ciento). MS (ESI): 226.2 $[M+H]^+$.

288

Síntesis de triclorhidrato de (R)-1-[2-(4-amino-piperidin-1-il)-etil]-piperidin-3-ol (12) (esquema de reacción 2):



(1) Terbutiléster del ácido {1-[2-((R)-3-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-carbámico (13)

Se prepara de una manera análoga al 9, empezado a partir del terbutil-éster 8 (3.52 gramos, 14.41 milimoles), clorhidrato de (R)-3-hidroxi-piperidina (2.18 gramos, 15.85 milimoles), DIEA (5.6 mililitros, 33.14 milimoles), y yoduro de cianometil-trimetil-fosfonio (4.2 gramos, 17.29 milimoles).

Rendimiento: 3.53 gramos (36 por ciento). MS (ESI): 328.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.61 (br d, 1H), 3.89 (m, 3H), 3.53 (m, 1H), 3.03 (m, 2H), 2.55-2.73 (m, 6H), 2.44 (m, 1H), 2.3 (m, 2H), 1.83-2.02 (m, 3H), 1.5-1.7 (m, 4H), 1.44 (s, 9H).

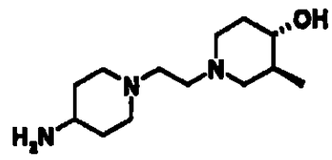
(2) Triclorhidrato de (R)-1-[2-(4-amino-piperidin-1-il)-etil]-piperidin-3-ol (12)

Se prepara mediante la disociación con BOC de terbutil-éster 13 (1.7 gramos, 5.19 milimoles) con HCl 4M en dioxano (10.4 mililitros, 41.52 milimoles), como se describe para la amina 7.

Rendimiento: 1.69 gramos (96 por ciento). MS (ESI): 228.3 $[M+H]^+$.

Síntesis de triclorhidrato de (3S,4S)-1-[2-(4-amino-piperidin-1-il)-etil]-3-metil-piperidin-4- l (14)

289



(1) (3S,4S)-1-[2-(4-terbutoxi-carbonilamino-piperidin-1-il)-etil]-3-metil-piperidin-4-il)-etil]-3-metil-piperidin-4-iléster del ácido 2,2-dimetil-propiónico (15)

Una solución del terbutil-8 (4.8 gramos, 19.65 milimoles) y trietilamina (4.1 mililitros, 29.47 milimoles) en 150 mililitros de DCM, se enfría a -78°C. Se agrega lentamente anhídrido tríflico (4.3 mililitros, 25.54 milimoles), y se continúa la agitación durante 1 hora. Luego la mezcla se deja calentar a 0°C, y se agrega una solución de 3S-metil-piperidin-4S-iléster del ácido 2,2-dimetil-propiónico 17, para la preparación ver más adelante (3.72 gramos, 18.66 milimoles), en 20 mililitros de DCM a 0°C. La agitación se continúa a temperatura ambiente durante 1 hora. La mezcla se lava dos veces con agua, se seca sobre sulfato de sodio, se filtra, y se evapora.

Rendimiento: 9.3 gramos (>100 por ciento, contuvo algo de trietilamina). MS (ESI): 426.3 $[M+H]^+$.

(2) Terbutiléster del ácido {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-carbámico (16)

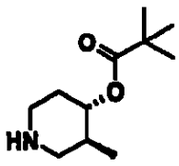
El 15 crudo (8.2 gramos, 192ç.27 milimoles) se trata con NaOMe (0.5 en metanol, 77 mililitros, 38.5 milimoles), y se calienta bajo reflujo durante 24 horas. Luego se evapora el solvente, se recupera el residuo en DCM, y se extrae con NaOH 1N y salmuera.

El secado y la evaporación dieron un aceite castaño, el cual se purifica mediante cromatografía sobre gel de sílice utilizando DCM (saturado con amoniaco) y MeOH (del 1 por ciento al 5 por ciento). Rendimiento: 3.07 gramos (46 por ciento). MS (ESI): 342.3 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.51 (br d, 1H), 3.5 (br m, 1H), 3.17 (td, 1H), 2.85-3.08 (m, 4H), 2.63 (m, 4H), 2.1-2.35 (m, 3H), 1.48-2.04 (m, 9H), 1.42 (s, 9H), 0.99 (d, 3H).

(3) Triclorhidrato de (3S,4S)-1-[2-(4-amino-piperidin-1-il)-etil]-3-metil-piperidin-4-ol (14)

Se prepara mediante la disociación con BOC de terbutil-éster 16 (3.07 gramos, 8.98 milimoles) con HCl 4M en dioxano (11.2 mililitros, 44.8 milimoles) como se describe para la amina 7. Rendimiento: 3.1 gramos (98 por ciento). MS (ESI): 328.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.61(br d, 1H), 3.89 (m, 3H), 3.53 (m, 1H), 3.03 (m, 2H), 2.55-2.73 (m, 6H), 2.44 (m, 1H), 2.3 (m, 2H), 1.83-2.02 (m, 3H), 1.5-1.7 (m, 4H), 1.44 (s, 9H).

Síntesis de (3S,4S)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (17) (esquema de reacción 2):



(1) Paso A: 1-bencil-3-metil-piperidin-4-il-éster del ácido trans-2,2-dimetil-propiónico (18).

A una mezcla *cis/trans* de 1-bencil-3-metil-piperidin-4-ol (50

gramos, 243 milimoles, preparada como se describe en *Can. J. Chem.* (1972) 50, 803) en tetrahidrofurano, se le agrega trietilamina (51 mililitros, 365 milimoles), seguida por cloruro de 2,2-dimetil-propionilo (45 mililitros, 365 milimoles). La reacción es exotérmica, y se forma un precipitado. La mezcla se calienta bajo reflujo durante 18 horas, se enfría, se filtra, y se lava con éter. Las capas orgánicas se lavan con NaOH 1N y salmuera, se secan, y se evaporan. El crudo se purifica mediante cromatografía sobre gel de sílice utilizando hexano y EtOAc (5 por ciento), para dar el isómero-*trans* puro como un aceite incoloro.

Rendimiento: 38 gramos (54 por ciento). MS (ESI): 290.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.3 (m, 5H), 4.29 (td, 1H), 3.45 (d, 2H), 2.74 (d, 2H), 2.05 (td, 1H), 1.8 (m, 3H), 1.46 (m, 1H), 1.14 (s, 9H), 0.8 (d, 3H).

(2) Paso B: 3-metil-piperidin-4-il-éster del ácido *trans*-2,2-dimetil-propiónico (19)

El éster-*trans* 18 (104 gramos, 359 milimoles) se hidrogena en metanol (1700 mililitros) con Pd/C en la presencia de un equivalente de HCl (431 mililitros, 359 milimoles, 1.25M en MeOH). La mezcla se filtra y se evapora. El residuo se vuelve a disolver en éter, y se extrae con NaOH 1N y salmuera. La evaporación da un aceite incoloro.

Rendimiento: 62.7 gramos (87 por ciento). MS (ESI): 200.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.46 (td, 1H), 3.06 (m, 2H), 2.68 (td, 1H), 2.35 (m, 1H), 1.94 (m, 1H), 1.68 (m, 2H), 1.34-1.46 (m, 1H), 1.2 (s,

292

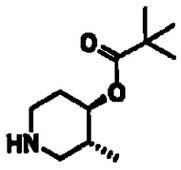
9H), 0.96 (d, 3H).

(3) Paso C: (3S,4S)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (17).

El 19 racémico (62.7 gramos, 314.4 milimoles) se disuelve en EtOAc (300 mililitros), y se agrega una solución de ácido L-(-)-O,O'-dibenzoil-tartárico (56.3 gramos, 157.2 milimoles) en EtOAc (450 mililitros). El sólido formado se filtra, se lava con EtOAc frío y se seca. Luego se recristaliza a partir de metanol caliente (400 mililitros). Los cristales se recolectan, y la base libre se libera mediante su tratamiento con NaOH 1N y su extracción con éter

Rendimiento: 13 gramos (21 por ciento). MS y 1H-RMN son idénticas al 19 racémico. $[\alpha]_D$ = 65.1 (c=1 en MeOH).

Síntesis de (3R,4R)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (20):

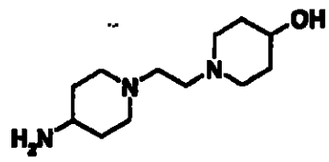


El licor madre del 17 anterior, se trata con NaOH 1N, para obtener la base libre, la cual luego se cristaliza con ácido D-(+)-O,O'-dibenzoil-tartárico como se describe anteriormente, para el antípoda 20.

Rendimiento: 16 gramos (25 por ciento). MS y 1H-RMN son idénticas al 19 racémico. $[\alpha]_D$ = 64.7 (c=1 en MeOH).

293

Síntesis de triclorhidrato de 1-[2-(4-amin -piperidin-1-il)-etil]-piperidin-4-ol (21) (esquema de reacción 3):



(1) 1-(2-hidroxi-etil)-piperidin-4-ol (22)

Se disuelve piperidin-4-ol (5 gramos, 49.4 milimoles) en 200 mililitros de etanol, y se agrega carbonato de sodio anhidro (21 gramos, 197.6 milimoles). Se agrega por goteo 2-bromo-etanol (6.9 mililitros, 98.8 milimoles) y la mezcla de reacción se pone a reflujo durante 16 horas. Después de la evaporación bajo presión reducida, la mezcla se agita con 200 mililitros de DCM, y se filtra. El filtrado transparente se evapora bajo presión reducida, y se seca en un alto vacío.

Rendimiento: 4.3 gramos (60 por ciento) de un aceite incoloro.

MS (ESI): 146 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.52 (d, 1H), 4.32 (t, 1H), 3.48 (dt, 2H), 3.4 (m, 1H), 2.7 (m, 2H), 2.35 (t, 2H), 2.05 (m, 2H), 1.68 (m, 2H), 1.3-1.4 (m, 2H).

(2) Terbutiléster del ácido {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-}-carbámico (23)

El terbutil-éster del ácido piperidin-4-il-carbámico 3 (5 gramos, 25 milimoles), 1-(2-hidroxi-etil)-piperidin-4-ol 22 (4 gramos, 27.5 milimoles) y DIEA (5.6 mililitros, 32.5 milimoles) se suspenden en 25 mililitros de propionitrilo. Se agrega yoduro de cianometil-trimetil-

294
295

fosfonio (4 gramos, 30 milimoles), y la mezcla de reacción se pone a reflujo. Se agregan adicionales de cianometil-trimetil-fosfonio (1.5 gramos, 11.25 milimoles) después de 90 minutos y después de 3 horas. Después de enfriar a temperatura ambiente, se agrega una solución de carbonato de potasio (4 gramos) en 250 mililitros de agua, y el producto se aisla mediante extracción con DCM. La evaporación bajo presión reducida dio 6.9 gramos de un aceite rojo, el cual se pudo cristalizar a partir de éter.

Rendimiento: 2.2 gramos (27 por ciento) de cristales incoloros.

MS (ESI): 328 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.72 (br d, 1H), 4.5 (d, 1H), 3.42 (m, 1H), 3.2 (m, 1H), 2.8 (m, 2H), 2.7 (m, 2H), 2.35 (m, 4H), 2.0 (dt, 2H), 1.9 (dt, 2H), 1.68 (m, 4H), 1.4 (s, 9H), 1.35 (m, 4H.

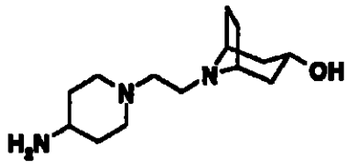
(3) triclorhidrato de 1-[2-(4-amino-piperidin-1-il)-etil]-piperidin-4-ol (21)

El éster 23 (2.2 gramos, 6.72 milimoles) se disuelve en HCl 4M en dioxano a 0°C, y se agita a temperatura ambiente durante 3 horas. Después de la evaporación del solvente, el producto se seca en un alto vacío.

Rendimiento: 2.3 gramos (100 por ciento) de un sólido blanco. MS (ESI): 228 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 5 (m, 1H), 3.4 (m, 4H), 2.7 (m, 4H), 24 (m, 2H), 1.85-2.0 (m, 4H), 1.65 (m, 4H), 1.35 (m, 4H), 1.2 (m, 2H).

Síntesis de triclorhidrato de 8-[2-(4-amino-piperidin-1-il)-etil]-8-aza-biciclo[3.2.1]octan-3-ol (24) (esquema de reacción 3):

295



(1) 8-(2-hidroxi-etil)-8-aza-biciclo[3.2.1]octan-3-ol (25)

El clorhidrato de 8-aza-biciclo[3.2.1]octan-3-ol (5.1 gramos, 31.45 milimoles) y carbonato de sodio (13.3 gramos, 125.8 milimoles) se suspenden en 150 mililitros de etanol a temperatura ambiente. Se agrega por goteo 2-bromo-etanol (4.4 mililitros, 62.9 milimoles) dentro de 20 minutos, y la mezcla de reacción se pone a reflujo durante 15 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se evapora bajo presión reducida. La mezcla se agita con 200 mililitros de DCM, y se filtra. El filtrado transparente se seca sobre sulfato de sodio anhidro, se filtra, se evapora bajo presión reducida, y se seca en un alto vacío.

Rendimiento: 5.4 gramos (100 por ciento) de un aceite incoloro.

MS (ESI): 172 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.25 (d, 2H), 3.78 (t, 1H), 3.42 (t, 2H), 3.06 (m, 2H), 2.36 (t, 2H), 2.03 (m, 2H), 1.85 (m, 2H), 1.75 (m, 2H), 1.55 (d, 2H).

(2) Terbutiléster del ácido {1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-carbámico (26)

El terbutil-éster del ácido piperidin-4-il-carbámico 3 (1 gramo, 5 milimoles), 8-(2-hidroxi-etil)-8-aza-biciclo[3.2.1]octan-3-ol 25 (1 gramo, 5.5 milimoles), y DIEA (1.1 mililitros, 6.5 milimoles), se disuelven en 5 mililitros de propionitrilo. Se agrega yoduro de

296

cianometil-trimetil-fosfonio (792 miligramos, 6 milimoles) con agitación, y la mezcla de reacción se pone a reflujo, el cual es seguido por cromatografía de capa delgada. Se agrega yoduro de cianometil-trimetil-fosfonio adicional (400 miligramos) después de 2 horas, y la mezcla se pone a reflujo durante otra hora. Después de enfriar a temperatura ambiente, DCM. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre anhidro, y se agrega una solución de carbonato de potasio (4 gramos) en 250 mililitros de agua, y el producto se aísla mediante extracción con sulfato de sodio, se filtra, y se evapora bajo presión reducida. El producto crudo (1.9 gramos) se cristaliza a partir de éter.

Rendimiento: 940 miligramos (53 por ciento) de cristales beiges claros. MS (ESI): 354 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.73 (br d, 1H), 4.25 (d, OH), 3.8 (m, 1H), 3.17 (m, 1H), 3.08 (m, 2H), 2.8 (m, 2H), 2.35 (m, 4H), 2.0 (m, 2H), 1.92 (m, 2H), 1.85 (dt, 2H), 1.78 (m, 2H), 1.65 (m, 2H), 1.53 (m, 2H), 1.38 (s, 9H), 1.33 (m, 2H).

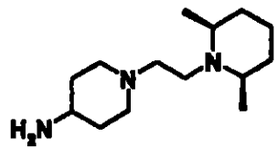
(3) Triclorhidrato de 8-[2-(4-amino-piperidin-1-il)-etil]-8-aza-biciclo[3.2.1]octan-3-ol (24)

El éster 26 (4.5 gramos, 12.73 milimoles) se disuelve en HCl 4M en dioxano a 0°C, y se agita a temperatura ambiente durante 3 horas. Después de la evaporación de solvente, el producto se seca en un alto vacío.

Rendimiento: 4.6 gramos (100 por ciento) de un sólido blanco. MS (ESI): 254 $[M+H]^+$.

297

Síntesis de tricl rhidrato de 1-[2-((2S,6R)2,6-dimetil-piperidin-1-il)-etil]-piperidin-4-llamina (27) (esquema de reacción 3):



(1) Terbutil-éster del ácido {1-[2-(2,6-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-carbámico (28)

El compuesto 28 se prepara de una manera análoga al 25, empezando a partir de cis-2,6-dimetil-piperidina (6.4 mililitros, 44.17 milimoles) y bromoetanol (6.1 mililitros, 88.33 milimoles).

Rendimiento: 3.9 gramos (56 por ciento) de un aceite amarillo. MS (ESI): 158.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.48 (br, 1H), 3.4 (t, 2H), 2.6 (t, 2H), 24 (m, 2h), 1.1-1.6 (M, 6h), 1.03 (D, 6h).

(2) Terbutiléster del ácido {1-[2-(2,6-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-carbámico (29)

El compuesto 29 se prepara de una manera análoga al 26, empezando a partir del compuesto 28 (3.85 gramos, 24.48 milimoles) y terbutil-éster del ácido piperidin-4-il-carbámico 3 (4.46 gramos, 22.25 milimoles).

Rendimiento: 6.16 gramos (82 por ciento) de un aceite amarillo. MS (ESI) 340.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.73 (br d, 1H), 3.18 (m, 1H), 2.75 (m, 2H), 2.65 (m, 2H), 2.35 (m, 2H), 2.25 (m, 2H), 1.92 (m, 2H), 1.65 (m, 2H), 1.57 (m, 2H), 1.49 (m, 2H), 1.38 (s, 9H), 1.35 (m, 2H), 1.12 (m, 2H), 1.03 (d, 6H).

(3) Tricl rhidrato de 1-[2-((2S,6R)-2,6-dimetil-piperidin-1-il)-

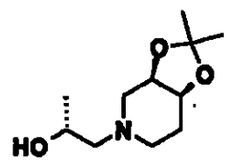
298
994

etil]-piperidin-4-ilamina (27)

El compuesto 27 se prepara de una manera análoga al 24, empezando a partir del derivado protegido con BOC 29 (6.16 gramos, 18.14 milimoles).

Rendimiento: 6.3 gramos (100 por ciento) de un sólido blanco. MS 8ESI): 240.3 $[M+H]^+$.

Síntesis de (R)-1-((3a,7a)-2,2-dimetil-tetrahidro-[1,3]dioxolo[4,5-c]piridin-5-il)-propan-2-ol (30) (esquema de reacción 4):



(1) Bencil-éster del ácido 3,6-dihidro-2H-piridin-1-carboxílico (31)

La 1,2,3,6-tetrahidro-piridina (3 gramos, 36.1 milimoles) se trata con carbonato de sodio acuoso al 10 por ciento (2.1 mililitros), y se enfría a 0°C. Dentro de 1 hora, se agrega por goteo cloroformiato de bencilo (cloruro-Z, 5.1 mililitros, 36 milimoles) dentro de 1 hora. Después de una agitación adicional durante 2 horas, la mezcla se trata con 30 mililitros de salmuera, y se extrae cuatro veces con dietil-éter. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo, 7 gramos de un aceite incoloro, se purifica mediante cromatografía por evaporación (gel de sílice, ciclohexano/acetato de etilo, 9:1).

Rendimiento: 3.63 gramos (46 por ciento) de un aceite incoloro. MS

(ESI): 218 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 7.28-7.4 (m, 5H), 5.83 (m, 1H), 5.66 (m, 1H), 5.15 (s, 2H), 3.95 (m 2H), 3.58 (t, 2H), 2.15 (m, 2H).

(2) Bencil-éster del ácido 3,4-dihidroxi-piperidin-1-carboxílico (32)

El 31 (3.63 gramos, 16.7 milimoles) se disuelve en 16 mililitros de una mezcla de 1:1 de agua y acetona. Después de la adición de N-óxido de N-metil-morfolina (2.9 gramos, 24.8 milimoles), se agrega una solución al 1 por ciento de tetróxido de osmio en terbutanol (7.23 mililitros, 0.28 milimoles). La mezcla se agita a temperatura ambiente durante 20 horas. Luego se agregan 70 mililitros de una solución saturada de bisulfito de sodio. Después de 15 minutos de agitación a temperatura ambiente, la mezcla de reacción se extrae con acetato de etilo. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo, 4.7 gramos de un aceite amarillo, se purifica mediante cromatografía por evaporación (gel de sílice, acetato de etilo).

Rendimiento: 3.83 gramos (91 por ciento). MS (ESI): 252 $[M+H]^+$, 1H-RMN (CDC_3): δ (ppm) 7.27-7.4 (m, 5H), 5.13 (s, 2H), 3.88 (m, 1H), 3.79 (m, 2H), 3.66 (m, 2H), 3.5 (dd, 1H), 3.34 (m, 1H), 2.13 (m, 2H), 1.82 (m, 1H), 1.7 (m, 1H).

(3) Bencil-éster del ácido 22-dimetil-tetrahidro-[1,3]dioxolo[4,5-c]piridin-5-carboxílico (33)

El 32 anterior (3.72 gramos, 14.8 milimoles) se disuelve en 20 mililitros de diclorometano. Después de la adición de 2,2-

dimetoxipropano (3.6 mililitros, 30 milimoles) y ácido p-toluensulfónico (141 miligramos, 0.7 milimoles), la mezcla se agita a temperatura ambiente durante 4 horas. Luego la mezcla se diluye con 30 mililitros de diclorometano, se lava subsecuentemente con NaOH 1N y salmuera, se seca sobre sulfato de sodio, y se evapora. El producto racémico crudo, 4.32 gramos de un aceite amarillo, se separa en sus enantiómeros mediante HPLC quiral (Chiralcel, OJ, 20 micras, hexano/isopropanol, 9:1).

Rendimiento: 810 miligramos pico 1, y 942 miligramos (pico 2) (40 por ciento). MS (ESI): 292.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 7.25-7.4 (m, 5H), 5.14 (s, 2H), 4.18-4.4 (m, 2H), 3.7-3.82 (m, 1H), 3.38-3.58 (m, 3H), 1.74-2.0 (m, 2H), 1.44 (s, 3H), 1.35 (s, 3H).

(4) 2,2-dimetil-hexahidro-[1,3]dioxolo[4,5-c]piridina (34) (único enantiómero-*cis*, configuración absoluta desconocida).

El 33 (pico 1 del anterior) (450 miligramos, 1.54 milimoles) se disuelven en 10 mililitros de metanol. Después de la adición de paladio al 10 por ciento sobre carbono (45 miligramos), la mezcla se hidrogena a temperatura ambiente durante 20 horas. Luego la mezcla se filtra sobre Celite. La evaporación dio 240 miligramos (99 por ciento) de un aceite incoloro.

MS (ESI): 158.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.25 (m, 1H), 4.12 (m, 1H), 2.9-3.1 (m, 3H), 2.78 (m, 1H), 1.85-2.40 (m, 3H), 1.52 (s, 3H), 1.38 (s, 3H).

(5) 1-(2,2-dimetil-tetrahidro-[1,3]dioxolo[4,5-c]piridin-5-il)-pr pan-2ol (30) (único enantiómer , configuraci n absoluta de

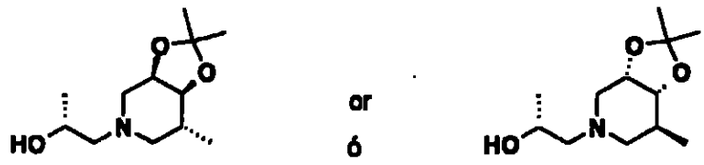
301

dioxol desconocida).

Se disuelven el 34 (90 miligramos, 0.57 milimoles), (R)(+)-óxido de propileno (166 miligramos, 2.8 milimoles), y trietilamina (160 microlitros, 1.1 milimoles) en 2 mililitros de etanol, y se agitan a temperatura ambiente durante 4 horas. La mezcla de reacción se diluye con 20 mililitros de acetato de etilo, se lava subsecuentemente con NaOH 1N y salmuera, se seca sobre sulfato de sodio, y se evapora. El producto crudo, 100 miligramos de un aceite amarillo, se purifica mediante cromatografía por evaporación (gel de sílice, diclorometano/metanol/amoniaco, 95:5:0.5).

Rendimiento: 70 miligramos (70 por ciento). MS (ESI): 216.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.03-4.28 (m, 2H), 3.9 (m, 1H), 2.2-3.08 (m, 6H), 1.36-2.13 (m, 3H), 1.51 (s, 3H), 1.38 (s, 3H), 1.12-1.22 (dd, 3H).

Síntesis de (R)-1-(2,2,7-trimetil-tetrahidro-[1,3]dioxolo[4,5-c]piridin-5-il)-propan-2-ol (35) (esquema de reacción 5):



(1) 1-bencil-3-(R,S)-metil-1,2,3,6-tetrahidro-piridin-4-il-éster del ácido trifluoro-metansulfónico (36)

Una solución de bis-(trimetilsilil)-amida de litio 1M en tetrahidrofurano (540 microlitros, 0.54 milimoles), se diluye con 1 mililitro de tetrahidrofurano, y se enfría a -78°C. Se agrega una

302

solución de 1-bencil-3-metil-4-piperidona (100 miligramos, 0.49 milimoles) en 0.5 mililitros de tetrahidrofurano con una jeringa dentro de 5 minutos. Después de agitar durante 2 horas a esta temperatura, se agrega una solución de N-fenil-trifluorometansulfonimida (188 miligramos, 0.52 milimoles) en 1 mililitro de tetrahidrofurano dentro de 10 minutos. La suspensión beige se agita durante otras 4 horas a 0°C. La solución amarilla se apaga con 1 mililitro de una solución saturada de cloruro de amonio, se diluye con agua helada, y se extrae tres veces con acetato de etilo. Las capas orgánicas se lavan con salmuera, se secan sobre sulfato de sodio, y se evaporan. El producto crudo, 311 miligramos de un aceite amarillo, se purifica mediante cromatografía por evaporación (gel de sílice, ciclohexano/acetato de etilo, 4:1).

Rendimiento: 127 miligramos (77 por ciento) de un aceite incoloro. MS (ESI): 336 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.22-7.36 (m, 5H), 5.89 (dd, 1H), 3.54-3.65 (m, 2H), 3.05 (br s, 2H), 2.75 (m, 1H), 2.59 (m, 1H), 2.32 (m, 1H), 1.06 (d, 3H).

(2) 1-bencil-3-(R,S)-metil-1,2,3,6-tetrahidro-piridina (37)

El 36 anterior (100 miligramos, 0.3 milimoles), acetato de paladio(II) (1.34 miligramos, 6 micromoles), trifenilfosfina (31 miligramos, 12 micromoles), y trietilamina (125 microlitros, 0.9 milimoles), se disuelven en 1 mililitro de N,N-dimetilformamida. Después de la adición de ácido fórmico (22.5 microlitros, 0.6 milimoles), la mezcla se agita durante 1 hora a 60°C. La mezcla de reacción se diluye con acetato de etilo, se lava subsecuentemente

303

con NaOH 1N y salmuera, se seca sobre sulfato de sodio, y se evapora. El producto crudo, 78 miligramos de un aceite amarillo, se purifica mediante cromatografía por evaporación (gel de sílice, ciclohexano/acetato de etilo, 3:1).

Rendimiento: 42 miligramos (75 por ciento) de un aceite amarillo. MS (ESI): 188.2 $[M+H]^+$, 1H-RMN ($CDCl_3$). δ (ppm) 7.23-7.41 (m, 5H), 5.62 (s, 2H), 3.63 (br s, 2H), 3.12 (d, 1H), 2.83 (m, 2H), 2.48 (m, 1H), 2.02 (br s, 1H), 0.96 (d, 3H).

(3) (3RS,4SR,5RS)-1-bencil-5-metil-piperidina-3,4-diol (racémico) (38)

El 37 (570 miligramos, 3 milimoles) se disuelve en 10 mililitros de una mezcla de 1:1 de agua y acetona. Después de la adición de N-óxido de N-metil-morfolina (529 miligramos, 4.5 milimoles), se agrega una solución al 2.5 por ciento de tetróxido de osmio en terbutanol (527 microlitros, 52 micromoles). La mezcla se agita a temperatura ambiente durante 24 horas. Luego se agregan 10 mililitros de una solución saturada de bisulfito de sodio. Después de 15 minutos de agitación a temperatura ambiente, la mezcla de reacción se extrae con acetato de etilo. Las capas orgánicas se lavan subsecuentemente con NaOH 1N y salmuera, se secan sobre sulfato de sodio, y se evaporan. El producto crudo, 460 miligramos de un aceite castaño oscuro, se purifica mediante cromatografía por evaporación (gel de sílice, diclorometano/metanol/amoniaco, 95:5:0.5).

Rendimiento: 290 miligramos (43 por ciento) del diol *cis*, *tras* para el

304

grupo metilo y 20 miligramos (3 por ciento) del derivado todo-*cis*. MS (ESI): 222 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.17-7.32 (m, 5H), 4.21 (d, 1H), 4.04 (br d, 1H), 3.58 (m, 1H), 3.41 (dd, 2H), 3.02 (m, 1H), 2.62 (m, 1H), 2.56 (br d, 1H), 2.12 (br d, 1H), 1.69-1.88 (m, 2H), 0.86 (d, 3H).

(4) (3aRS,7RS,7aSR)-5-bencil-2,2,7-trimetil-hexahidro-[1,3]dioxolo[4,5-c]piridina (racémica) (39)

El 38 anterior (290 miligramos, 1.3 milimoles) se disuelve en 4 mililitros de diclorometano. Después de la adición en porciones de 2,2-dimetoxipropano (1.6 mililitros, 13 milimoles) y ácido p-toluensulfónico (300 miligramos, 1.6 milimoles), la mezcla se agita a temperatura ambiente durante 16 horas. Luego la mezcla se diluye con diclorometano, se lava subsecuentemente con NaOH 1N y salmuera, se seca sobre sulfato de sodio y se evapora. El producto crudo, 333 miligramos de un aceite amarillo, se purifica mediante cromatografía por evaporación (gel de sílice, ciclohexano/acetato de etilo, 3:1).

Rendimiento: 303 miligramos (89 por ciento). MS (ESI): 262.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 7.20-7.40 (m, 5H), 4.19 (br s, 1H), 3.69 (br s, 1H), 3.43-3.63 (m, 2H), 2.89 (m, 1H), 2.53 (m, 2H), 2.02 (m, 1H), 1.88 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 1.00 (d, 3H).

(5) (3aRS,7RS,7aSR)-5-bencil-2,2,7-trimetil-hexahidro-[1,3]dioxolo[4,5-c]piridina (racémica) (40).

El 39 anterior (250 miligramos, 0.96 milimoles) se disuelve en 5 mililitros de isopropanol. Después de la adición de paladio al 10 por

305

ciento sobre carbono (25 miligramos), la mezcla se hidrogena a temperatura ambiente durante 16 horas. Luego la mezcla se filtra sobre Celite. La evaporación dio 170 miligramos (100 por ciento) de un aceite incoloro.

MS (ESI): 172.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.05 (m, 1H), 3.67 (dd, 1H), 3.39 (d, 1H), 2.98 (m, 2H), 2.21 (t, 1H), 2.05 (m, 1H), 1.73 (m, 1H), 1.52 (s, 3H), 1.37 (s, 3H), 0.98 (d, 3H).

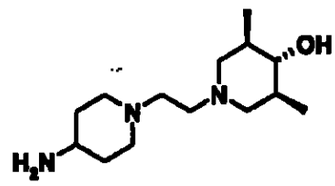
(6) 1-(2,2,7-trimetil-tetrahidro-[1,3]dioxolo[4,5-c]piridin-5-il)-propan-2-ol (35) (mezcla de diastereómeros).

Se disuelven el 40 (175 miligramos, 1 milimol), y trietilamina (285 microlitros, 2 milimoles) en 3 mililitros de etanol, y se agitan a temperatura ambiente durante 5 horas. Después de la evaporación, el residuo se disuelve en acetato de etilo, se lava subsecuentemente con NaOH 1N y salmuera, se seca sobre sulfato de sodio, y se evapora. El producto crudo, 214 miligramos de un aceite amarillo, se purifica mediante cromatografía por evaporación (gel de sílice, diclorometano/metanol/amoniaco, 95:5:0.5).

Rendimiento: 140 miligramos (60 por ciento). MS (ESI): 172.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.05 (m, 1H), 3.67 (dd, 1H), 3.39 (d, 1H), 2.98 (m, 2H), 2.21 (t, 1H), 2.05 (m, 1H), 1.73 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H), 0.98 (d, 3H).

Síntesis de triclorhidrato de (3R,4R,5S)-1-[2-(4-amino-piperidin1il)-etil]-3,5-dimetil-piperidin-4-ol (41) (esquema de reacción 6):

306



(1) **N'-[1-bencil-3-metil-piperidin-(4E)-iliden]-N,N-dimetil-hidrazina (42)**

La N,N-dimetil-hidrazina (3 mililitro, 39.3 milimoles) y 1-bencil-3-metil-piperidin-4-ona (4 gramos, 19.7 milimoles) se disuelven en 50 mililitros de etanol, y se ponen a reflujo durante 18 horas. La mezcla de reacción se evapora bajo presión reducida y se seca en un alto vacío.

Rendimiento: 4.8 gramos de un aceite pálido (99 por ciento). MS (ESI): 246 $[M+H]^+$, 1HRMN (DMSO-d_6): δ (ppm) 7.29 (m, 4H), 7.23 (m, 1H), 3.48 (m, 2H), 2.8 (m, 1H), 2.65 (m, 1H), 2.35-2.55 (m, 2H), 2.29 (s, 6H), 2.25 (m, 1H), 1.9-2.1 (m, 1H), 1.00 (d, 3H).

(2) **N'-(1-bencil-35-dimetil-piperidin-4-iliden)-N,N-dimetil-hidrazina (43)**

Se disuelve di-isopropil-amina (3.3 mililitros, 23.5 milimoles) en 20 mililitros de tetrahidrofurano, y se enfría a -5°C. Se agrega por goteo una solución 1.6M de n-butil-litio en tetrahidrofurano (14.7 mililitros, 23.5 milimoles) dentro de 10 minutos. Después de 10 minutos adicionales a -5°C, se agrega una solución del 42 (4.8 gramos, 19.6 milimoles)) en 30 mililitros de tetrahidrofurano dentro de 20 minutos (el color de la mezcla de reacción cambió a rojo). Ahora la solución se enfría a -78°C. Se agrega por goteo yoduro de

metilo (1.33 mililitros, 21.5 milimoles) dentro de 15 minutos, y la mezcla se deja calentar a temperatura ambiente durante la noche. Se agrega diclorometano, y la solución se lava con agua. La evaporación dio 5 gramos de un aceite incoloro, el cual se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, acetato de etilo/hexanos, 1:1).

Rendimiento: 1.7 gramos de un sólido blanco (33 por ciento). MS (ESI): 260 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.33 (m, 4H), 7.22 (m, 1H), 3.48 (m, 2H), 3.37 (m, 1H), 2.68 (m; 1H), 2.59 (m, 1H), 2.43 (m, 1H), 2.43 (m, 1H), 229 (s, 6H), 2.15 (m, 1H), 2.0 (m, 1H), 1.23 (d, 6H).

(3) 1-bencil-3,5-dimetil-piperidin-4-ona (44)

El 43 (1.7 gramos, 6.5 milimoles) se disuelve en una solución 1.25M de HCl en metanol (20 mililitros, 25 milimoles), y se pone a reflujo durante 1.5 horas. La mezcla de reacción se evapora bajo presión reducida, y se seca en un alto vacío. El residuo (1.7 gramos de un aceite incoloro) se disuelve en acetato de etilo, y se trata con NaOH 5M. Las capas orgánicas se evaporan bajo presión reducida.

Rendimiento: 1.4 gramos de un aceite incoloro (84 por ciento). MS (ESI): 218 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.3 (m, 4H), 7.25 (m, 1H), 3.58 (m, 2H), 3.07 (m, 2H), 2.68 (m, 2H), 1.97 (dd, 2H), 0.82 (d, 6H).

(4) 1-bencil-3,5-dimetil-piperidin-4-ol (45)

Se agrega borohidruro de sodio (121 miligramos, 3.2 milimoles) a una solución del 44 (1.4 gramos, 64 milimoles) en 15 mililitros de

308
409

metanol, y la mezcla se agita a temperatura ambiente durante 30 minutos. La mezcla se evapora, y el residuo se disuelve en acetato de etilo y se lava con agua.

Rendimiento: 1.4 gramos de un aceite incoloro (99 por ciento). MS (ESI): 220 $[M+H]^+$.

(5) (3S,4R,5R)-1-bencil-3,5-dimetil-piperidin-4-il-éster de ácido acético (46)

Se agrega DMAP (40 miligramos, 0.3 milimoles) a una solución del 45 (1.4 gramos, 6.4 milimoles) en 10 mililitros de piridina. Después de a adición de anhídrido acético (0.9 mililitros, 9.5 milimoles), la mezcla se agita a 110°C durante 2 horas. La mezcla se evapora, y el residuo se disuelve en diclorometano, y se lava con agua. La evaporación dio 1.6 gramos de un aceite incoloro, el cual se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, acetato de etilo/hexanos, 1:9).

Rendimiento: 0.7 gramos de un aceite incoloro (42 por ciento, fracción 1). MS (ESI) 262 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm 7.2-7.3 (m, 5H), 4.18 (dd, 1H), 3.42 (s, 2H), 2.8 (m, 2H), 2.05 (s, 3H), 1.7-1.8 (m, 4H), 0.72 (d, 6H).

(6) (3R,4R,5S)-3,5-dimetil-piperidin-4-il-éster del ácido acético (47)

Se coloca hidróxido de paladio sobre carbono (20 por ciento, 300 miligramos) en un matraz llenado con argón, y se cubre cuidadosamente con 25 mililitros de metanol. Se agrega una solución del 46 (0.7 gramos, 2.7 milimoles) en metanol, y la mezcla se

309

hidrogena a temperatura ambiente durante 15 horas. Después de la filtración sobre Celite, el filtrado se evapora y se seca bajo un alto vacío.

Rendimiento: 0.41 gramos de un aceite incoloro (89 por ciento). MS (ESI): 172 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.22 (dd, 1H), 2.8 (dd, 2H), 2.15 (dd, 2H), 2.05 (s, 3H), 1.5 (m, 2H), 0.7 (d, 6H).

(7) (3S,4R,5R)-1-[2-(4-terbutoxi-carbonilamino-piperidin-1-il)-etil]-3,5-dimetil-piperidin-4-il-éster del ácido acético (48).

Se disuelve en 47 (2.3 gramos, 13.4 milimoles) en 5 mililitros de propionitrilo, y después de la adición del 8 (33 gramos, 13.4 milimoles), la mezcla de yoduro de cianometil-trimetil-fosfonio (4.4 gramos, 33.6 milimoles) y N-etildi-isopropil-amina (11.5 mililitros, 67.1 milimoles) se pone a reflujo durante 24 horas (control con cromatografía de capa delgada). Luego la mezcla se evapora bajo presión reducida. El residuo se diluye con acetato de etilo, se lava con una solución de K_2CO_3 al 10 por ciento y NaCl, y se seca sobre Na_2SO_4.

Rendimiento: 3.3 gramos de un aceite castaño (62 por ciento). MS (ESI) 398 $[M+H]^+$.

(8) Terbutil-éster del ácido {1-[2-((3S,4R,5R)-4-hidroxi-3,5-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-carbámico (49)

El 48 (3.3 gramos, 8.3 milimoles) se disuelve en 100 mililitros de metanol, y después de la adición de polvo de NaOMe (2.2 gramos, 41.5 milimoles), la mezcla se pone a reflujo durante 6 horas (control con cromatografía de capa delgada). Entonces la mezcla se evapora

310

bajo presión reducida. El residuo se diluye con acetato de etilo, se lava con agua, y se seca sobre Na_2SO_4. La evaporación dio 3.1 gramos de un aceite castaño. El producto crudo se purifica mediante recristalización a partir de éter.

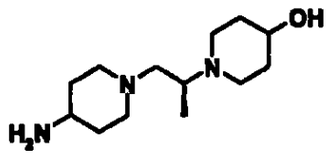
Rendimiento: 800 miligramos de un sólido incoloro (27 por ciento). MS (ESI): 356 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.7 (br d, 1H), 4.4 (d, 1H), 3.15 (br m, 1H), 2.75 (m, 4H), 2.4 (m, 1H), 2.3 (m, 4H), 1.9 (m, 2H), 1.3-1.7 (m, 8H), 1.38 (s, 9H), 0.85 (d, 6H).

(9) Triclorhidrato de (3R,4R,5S)-1-[2-(4-amino-piperidin-1-il)-etil]-3,5-dimetil-piperidin-4-ol (41)

El 49 se disuelve en una solución 4M de HCl en dioxano (20 mililitros), y se agita durante 4 horas (control con cromatografía de capa delgada) a temperatura ambiente. Luego la mezcla se enfría a 0°C y se filtra. El residuo se lava con éter. La evaporación dio 510 miligramos (89 por ciento) de cristales grises.

MS (ESI): 256 $[M+H]^+$.

Síntesis de triclorhidrato de 1-[(S)-2-(4-amino-piperidin-1-il)-1-metil-etil]-piperidin-4-ol (50) (esquema de reacción 7):



(1) 1-bencil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (51)

Una solución de 1-bencil-piperidin-4-ol (25 gramos, 130.7

311

milimoles) y trietilamina (36.1 mililitros, 261.4 milimoles) en 250 mililitros de tetrahidrofurano, se trata con cloruro de 2,2-dimetil-propionilo (32.2 mililitros, 261.4 milimoles). La suspensión se calienta bajo reflujo durante la noche. El solvente se evapora, el residuo se recupera en DCM, y se lava con una solución saturada de bicarbonato de sodio, y salmuera. El secado y la evaporación dieron un aceite naranja.

Rendimiento: 38.3 gramos (100 por ciento crudo). MS (ESI): 276 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 7.31 (m, 4H), 7.25 (m, 1H), 4.79 (m, 1H), 3.5 (s, 2H), 2.61 (m, 2H), 2.32 (m, 2H), 1.86 (m, 2H), 1.69 (m, 2H), 1.18 (s, 9H).

(2) piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (52)

Una solución de la piperidina 51 (35.99 gramos, 130.7 milimoles) en metanol, se hidrogena con Pd/C en la presencia de un equivalente de HCl (104.5 mililitros, 130.7 milimoles, 1.25M en MeOH). Después de la filtración y la evaporación, el crudo se recupera en éter, y se lava con NaOH 1N y salmuera. El secado, la evaporación, y la destilación (0.08 mbar, 75-90°C) dieron un aceite incoloro. Rendimiento: 17.98 gramos (74 por ciento).

MS (ESI): 186 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 9.22 (br s, 1H), 4.89 (m, 1H), 3.08 (m, 4H), 1.99 (m, 2H), 1.78 (m, 2H), 1.15 (s, 9H).

(3) 1-((R)-2-hidroxi-propil)-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (53)

Una solución de la piperidina 52 (2 gramos, 10.8 milimoles) y (R)-2-metil-oxirano (3.78 mililitros, 54 milimoles) en 2 mililitros de

312

etanol, se agita durante 24 horas en un matraz cerrado. El solvente se evapora, y el solvente se destila en un aparato Kugelrohr (0.08 mbar, 75-90°C).

Rendimiento: 2.58 gramos (98 por ciento).

MS (ESI): 244.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.65 (m, 1H), 4.1 (br s, 1H), 3.72 (m, 1H), 2.55 (m, 2H), 2.31 (m, 2H), 2.23 (m, 1H), 2.14 (m, 1H), 1.75 (m, 2H), 1.55 (m, 2H), 1.14 (s, 9H), 1.03 (d, 3H), $[\alpha]_D$ = 23.1 (c=1 en MeOH).

(4) 1-[(S-2-(4-terbutoxi-carbonil-amino-piperidin-1-il)-1-metil-etil]-piperidin-4-il-éster (54)

Una solución del alcohol 53 (1.26 gramos, 5.16 milimoles) y trietilamina (1.43 mililitros, 10.32 milimoles) en 80 mililitros de DCM, se enfría a -78°C. Se agrega lentamente anhídrido tríflico (0.85 mililitros, 5.16 milimoles), y se continúa la agitación durante 1 hora. Luego la mezcla se deja calentar a 0°C, y se enfría de regreso hasta -78°C después de 15 minutos. Se agrega lentamente una solución de terbutil-éster del ácido piperidin-4-il-carbámico 3 (1.03 gramos, 5.16 milimoles) en 40 mililitros de DCM a -78°C. Después de terminarse la adición, se remueve el baño de enfriamiento, y la solución oscura se deja calentar a temperatura ambiente. La mezcla se lava dos veces con agua, se seca sobre sulfato de sodio, se filtra, y se evapora. El crudo se purifica mediante cromatografía sobre gel de sílice utilizando DCM (saturada con amoniaco) y MeOH (1 por ciento).

Rendimiento: 1.7 gramos (77 por ciento).

MS (ESI): 426.3 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.74 (m, 1H), 4.43

313

(m, 1H), 3.43 (br m, 1H), 2.89 (m, 1H), 1.97-2.82 (m, 11H), 1.87 (m, 4H), 1.64 (m, 2H), 1.43 (s, 9H), 1.38 (m, 1H), 1.19 (s, 9H), 1.0 (d, 3H). $[\alpha]_D$ = 9.3 (c=1 en MeOH).

(5) Terbutil-éster del ácido {1-[(S)-2-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-carbámico (55)

El éster 54 anterior (1.7 gramos, 3.52 milimoles) se trata con NaOMe (0.5M en metanol, 21 mililitros, 10.5 milimoles), y se calienta bajo reflujo durante 24 horas. Luego se evapora el solvente, el residuo se recupera en DCM, y se extrae con NaOH 1N y salmuera. Después del secado y la evaporación, el crudo se purifica mediante cromatografía sobre gel de sílice utilizando DCM (saturada con amoniaco) y MeOH (del 1 por ciento al 3 por ciento), para dar un polvo blanco.

Rendimiento: 0.77 gramos (56 por ciento). MS (ESI): 342.3 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.43 (m, 1H), 3.64 (m, 1H), 3.43 (m, 1H), 2.88 (m, 1H), 2.75 (m, 4H), 1.8-245 (m, 10H) 1.3-1.65 (m, 5H), 1.44 (s, 9H), 0.99 (d, 3H). $[\alpha]_D$ = -15.3 (c=1 en MeOH).

(6) Triclorhidrato de 1-[(S)-2-(4-amino-piperidin-1-il)-1-metil-etil]-piperidin-4-ol (50)

Se prepara mediante disociación con BOC del terbutil-éster 55 (0.666 gramos, 1.95 milimoles) con HCl 4M en dioxano (2.93 mililitros, 11.72 milimoles), como se describe para la amina 7.

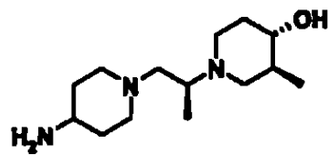
Rendimiento: 0.64 (93 por ciento). MS (ES): 242.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 10.5-10.85 (br m, 2H), 8.3-88 (br m, 3H), 2.75-4.15 (br m, 15H), 1.6-23 (br m, 7H), 1.39 (d, 3H). $[\alpha]_D$ = +13.2 (c=1

314

en MeOH).

Síntesis de triclorhidrato de (3S,4S)-1-[(S)-2-(4-amino-piperidin-1-il)-1-metil-etil]-3-metil-piperidin-4-ol (56)

(esquema de reacción 7):



(1) (3S,4S)-1-((R)-2-hidroxi-propil)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (57).

Una solución de la piperidina 17 (2 gramos, 10.8 milimoles) y (R)-2-metil-oxirano (3.78 mililitros, 54 milimoles) en 2 mililitros de etanol, se agita durante 24 horas en un matraz cerrado. El solvente se evapora, y el residuo se destila en un aparato Kugelrohr (0.08 mbar, 75-90°C).

Rendimiento: 2.58 (98 por ciento). MS (ESI): 258.2 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 4.39 (td, 1H), 3.82 (m, 1H), 2.95 (m, 1H), 2.76 (m, 1H), 2.42 (td, 1H), 2.17-2.33 (m, 2), 1.96 (m, 1H), 1.75-1.9 (m, 2H), 1.62 (m, 1H), 12 (s, 9H), 1.13 (d, 3H), 0.89 (d, 3H). $[\alpha]_D$ = 23.1 (c=1 en MeOH).

(2) (3S,4S)-1-[(S)-2-(4-terbutoxi-carbonil-amino-piperidin-1-il)-1-metil-etil]-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (58)

Una solución del alcohol 57 (1.26 gramos, 5.16 milimoles) y trietilamina (1.43 mililitros, 10.32 milimoles) en 80 mililitros de DCM,

315

se enfría a -78°C. Se agrega lentamente anhídrido tríflico (0.85 mililitros, 5.16 milimoles), y se continúa la agitación durante 1 hora. Luego la mezcla se deja calentar a 0°C, y se enfría de regreso a -78°C después de 15 minutos. Se agrega lentamente una solución de terbutiléster del ácido piperidin-4-il-carbámico, 3, (1.03 gramos, 5.16 milimoles) en 40 mililitros de DCM a -78°C. Después de completar la adición, se remueve el baño de enfriamiento, y la solución oscura se deja calentar a temperatura ambiente. La mezcla se lava dos veces con agua, se seca sobre sulfato de sodio, se filtra, y se evapora. El crudo se purifica mediante cromatografía sobre gel de sílice utilizando DCM (saturada con amoniaco) y MeOH (1 por ciento). Rendimiento: 1.7 gramos (77 por ciento). MS (ESI): 440.3 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 4.3 (td, 1H), 3.34 (m, 1H), 3.01 (m, 1H), 2.78-2.91 (m, 4H), 2.52 (dd, 1H), 2.42 (td, 1H), 2.02-2.3 (m, 4H), 1.94 (m, 1H), 1.84 (m, 3H), 1.5 (m, 3H), 1.45 (s, 9H), 1.21 (s, 9H), 1.04 (d, 3H), 0.9 (d, 3H). $[\alpha]_D$ = -9.3 (c=1 en MeOH).

(3) Terbutiléster del ácido {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-carbámico (59)

El éster 58 anterior (1.7 gramos, 3.52 milimoles) se trata con NaOMe (0.5M en metanol, 21 mililitros, 10.5 milimoles), y se calienta bajo reflujo durante 24 horas. Luego se evapora el solvente, se recupera el residuo en DCM, y se extrae con NaOH 1N y salmuera. Después del secado y la evaporación, el crudo se purifica mediante cromatografía sobre gel de sílice utilizando DCM (saturada con amoniaco) y MeOH (del 1 por ciento al 3 por ciento), para dar un

316

polvo blanco.

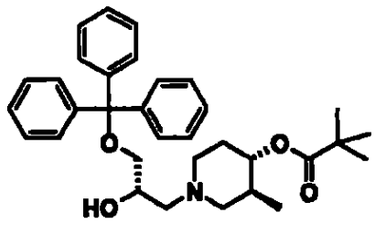
Rendimiento: 0.77 gramos (56 por ciento). MS (ESI): 356.3 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 4.86 (s, 1H), 3.32 (m, 1H), 2.94-3.06 (m, 2H), 2.72-2.87 (m, 3H), 2.49 (dd, 1H), 2.34 (td, 1H), 2.14-2.28 (m, 2H), 1.97-2.1 (m, 2H), 1.75-1.93 (m, 3H), 1.53 (m, 4H), 1.44 (s, 9H), 1.04 (d, 3H), 0.97 (d, 3H). $[\alpha]_D$ = 15.3 (c=1 en MeOH).

(4) Triclorhidrato de (3S,4S)-1-[(S)-2-(4-amino-piperidin-1-il)-1-metil-etil]-3-metil-piperidin-4-ol (56)

Se prepara mediante disociación con BOC del terbutil-éster 59 (0.666 gramos, 1.95 milimoles) con 4M-HCl en dioxano (2.93 mililitros, 11.72 milimoles), como se describe para la amina 7.

Rendimiento: 0.64 gramos (93 por ciento). MS (ESI): 256.2 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 4.25 (br m, 1H), 4.03 (br m, 3H), 3.05-3.9 (m, 9H), 1.95-2.55 (m, 7H), 1.54 (d, 3H), 1.1 (d, 3H). $[\alpha]_D$ = +13.2 (c=1 en MeOH).

Síntesis de (3S,4S)-1-((S)-2-hidroxi-3-tritiloxi-propil)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (60):



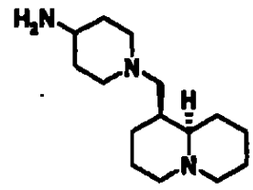
Se disuelven (S)-2-tritiloximetil-oxirano (636 miligramos, 2 milimoles) y (3S,4S)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico 17 (400 miligramos, 2 milimoles) en 7 mililitros de etanol,

317

y se agitan a temperatura ambiente durante 23 horas. La suspensión blanca se calienta a 40°C, y se agita durante 2 horas adicionales. La mezcla de reacción se evapora bajo presión reducida, y el producto crudo se purifica mediante cromatografía por evaporación (gel de sílice, acetato de etilo al 20 por ciento en ciclohexano).

Rendimiento: 681 miligramos (66 por ciento) de una espuma blanca. MS (ESI): 516.4 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 7.4 (d, 6H), 7.31 (dd, 6H), 7.23 (dd, 3H), 4.62 (d, 1H), 4.22 (m, 1H), 3.74 (m, 1H), 2.95 (d, 2H), 2.72 (m, 2H), 2.22-2.41 (m, 2H), 2.07 (m, 1H), 1.58-1.84 (m, 3H), 1.14 (s, 9H), 0.76 (d, 3H).

Síntesis de triclorhidrato de (1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il)amina (61) (esquema de reacción 8):



(1) Terbutil-éster del ácido {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-carbámico (62)

Se disuelve el 3 (3 gramos, 15 milimoles) en 150 mililitros de propionitrilo. Se agregan etildi-isopropil-amina (10.2 mililitros, 60 milimoles), (-)-lupinina (2.5 gramos, 15 milimoles), y yoduro de cianometil-trimetil-fosfonio (reactivo de Zaragoza , 7.3 gramos, 30 milimoles). La mezcla de reacción se calienta a 120°C, y se agita durante 22 horas. Luego la mezcla se evapora bajo presión reducida. El residuo se disuelve con acetato de etilo, se lava con una solución

de K_2CO_3 al 10 por ciento y NaCl, y se seca sobre Na_2SO_4. La evaporación dio 57 gramos de un aceite castaño. El producto crudo se purifica mediante cromatografía por evaporación (acetato de etilo, luego etanol/acetato de etilo) (4:6), gel de sílice).

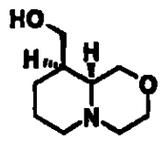
Rendimiento: 4.3 gramos (81.7 por ciento) de un aceite castaño. MS (ESI): 352 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 6.7 (br d, 1H), 3.2 (m, 1H), 2.7-2.75 (m, 4H), 2.4 (dd, 1H), 2.2 (dd, 1H), 1.38 (s, 9H), 1.15-2.0 (m, 20H).

(2) Triclorhidrato de 1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-ilamina (61)

El éster 62 (3.8 gramos, 10.8 milimoles) se disuelve en 15 mililitros de dioxano, y después de la adición de 70 mililitros de una solución 4M de HCl en dioxano, la mezcla se agita durante 4 horas a temperatura ambiente. El producto se filtra y se utiliza en el siguiente paso sin mayor purificación.

Rendimiento: 3.9 gramos (100 por ciento). MS (ESI): 252 $[M+H]^+$.

Síntesis de (9R,9aS)-1-(octahidro-pirido[2,1-c][1,4]oxazin-9-il)-metanol (racemato) (63) (esquema de reacción 9):



(1) 4-(3-bromo-propil)-morfolina-3,5-diona (64)

Una suspensión amarilla pálida de morfolina-3,5-diona (1.2 gramos, 10 milimoles), 1,3-dibromopropano (3.4 mililitros, 3.3 milimoles), y carbonato de potasio (2.7 gramos, 19 milimoles) en 23

319

mililitros de 2-butanona, se pone a reflujo bajo una atmósfera de argón durante 22 horas. Después de enfriarse, la suspensión se concentra sobre un evaporador giratorio, se vierte en hielo/agua, y se extrae dos veces con acetato de etilo. Las fases orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, y se evaporan. El aceite amarillo residual (2.06 gramos), se purifica mediante cromatografía (Biotage 40Mi, l = 15 centímetros, ciclohexano/acetato de etilo, 3:1).

Rendimiento: 1.24 gramos (52.5 por ciento) de un aceite incoloro. MS (EI): 235 $[M]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.37 (s, 4H), 3.95 (t, 2H), 3.39 (t, 2H), 218 (m, 2H).

(2) Etil-éster del ácido 4-oxo-1,3,4,6,7,8-hexahidro-pirido[2,1-c][1,4]oxazin-9-carboxílico

A una suspensión helada de hidruro de sodio (150 miligramos, 60 por ciento en aceite mineral, 3.75 milimoles) en 26 mililitros de tetrahidrofurano anhidro bajo argón, se le agrega una solución de fosfonoacetato de trietilo (0.31 mililitros, 1.5 milimoles) en 6 mililitros de tetrahidrofurano anhidro. La suspensión se agita a temperatura ambiente durante 2 horas, luego se agrega el 64 (354 miligramos, 1.5 milimoles) en 6 mililitros de tetrahidrofurano, y la mezcla resultante se pone a reflujo durante 10 horas. Después de enfriarse, la suspensión se concentra sobre un evaporador giratorio, se vierte sobre hielo/solución acuosa saturada de cloruro de amonio, y se extrae dos veces con acetato de etilo. Las fases orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio

320
321

anhidro, y se evaporan. El aceite amarillo residual (339 miligramos) se purifica mediante cromatografía (Biotage 12Mi, l = 15.5 centímetros, ciclohexano/acetato de etilo, 3:1).

Rendimiento: 60.3 miligramos (17.8 por ciento) de un aceite incoloro. MS (ESI): 226 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 4.94 (s, 2H), 4.27 (s, 2H), 3.75 (dd, 2H), 2.45 (m, 2H), 1.88 (m, 2H), 1.30 (t, 3H).

(3) Etiléster del ácido (9RS,9aSR)-4-oxo-octahidro-pirido[2,1-c][1,4]oxazin-9-carboxílico (racemato) (66)

Una solución del 65 (225 miligramos, 1.0 milimoles) en 5 mililitros de ácido acético, se hidrogena sobre 225 miligramos de dióxido de platino a temperatura ambiente y a presión normal durante 18 horas. Se agregan otros 225 miligramos de dióxido de platino, y se continúa la hidrogenación durante 24 horas. La suspensión negra se diluye con 10 mililitros de DCM, y se filtra a través de un cojín de Celite. El filtrado se evapora para dar 268 miligramos de un aceite amarillo, el cual se purifica mediante cromatografía (Biotage 12Si, l = 7.5 cm, acetato de etilo/etanol, 9:1).

Rendimiento: 144 miligramos (63.3 por ciento) de un aceite amarillo. MS (ESI): 228 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm), 4.45 (m, 1H), 4.00 (m, 2H), 3.9-3.75 (m, 4H), 3.60 (m, 1H), 2.65 (m, 1H), 2.55 (m, 1H), 1.90 (m, 2H), 1.75 (m, 1H), 1.45 (m, 1H), 116 (t, 3H).

(4) (9RS,9aSR)-1-(octahidro-pirido[2,1-c][1,4]oxazin-9-il)-metanol (racemato) (63)

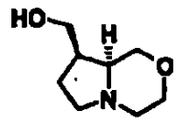
A una solución del 66 (114 miligramos, 0.5 milimoles) en 5 mililitros de tetrahidrofurano anhidro, se le agrega AH (40

321

miligramos, 1.0 milimoles), y la mezcla se pone a reflujo durante 9 horas. La mezcla se enfría a 0°C, y se trata sucesivamente con 0.04 mililitros de agua, hidróxido de sodio acuoso 3N (0.04 mililitros, 0.12 milimoles), y 0.12 mililitros de agua. La mezcla se agita durante 15 minutos, y luego se extrae tres veces con DCM. Las fases orgánicas combinadas se secan sobre sulfato de sodio anhidro, y se evaporan bajo presión reducida. El aceite amarillo pálido residual (75 miligramos) se purifica mediante cromatografía (Biotage, 12Si, l = 7.5 cm, DCM/MeOH/Amoniaco concentrado, 95:4.5:0.5).

Rendimiento: 35.1 (41.0 por ciento) de un aceite amarillo pálido. MS (ESI): 172 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.30 (br s, 1H), 3.65-3.55 (m, 4H), 3.50-3.35 (m, 2H), 2.70 (br d, 1H), 2.55 (br d, 1H), 2.10-1.95 (m, 2H), 1.5-1.60 (m, 2H), 1.60-1.50 (m, 2H), 1.35-120 (m, 2H).

Síntesis de (8R,8aS)-1-(hexahidro-pirrol[2,1-c][1,4]oxazin-8-il)-metanol (racemato) (67) (esquema de reacción 10):



(1) Etiléster del ácido 4-oxo-3,4,6,7-tetrahidro-1H-pirrolo[2,1-c][1,4]oxazin-8-carboxílico (68)

A una suspensión de hidruro de sodio (480 miligramos, 60 por ciento en aceite mineral, 12 milimoles) en 10 mililitros de tetrahidrofurano anhidro, se le agrega morfolina-3,5-diona (1.2 gramos, 10 milimoles) en 20 mililitros de tetrahidrofurano bajo una

322
323

atmósfera de argón. Después de 10 minutos, se agregan tetrafluoroborato de 1-carbetoxi-ciclopropil-trifenil-fosfonio (reactivo de Fuchs, 6.8 gramos, 11 milimoles) en 20 mililitros de tetrahidrofurano, y la mezcla se pone a reflujo durante 21 horas. Después de enfriarse, la suspensión se concentra sobre un evaporador giratorio, se vierte sobre hielo/solución saturada de bicarbonato de sodio, y se extrae tres veces con éter. Las fases orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, y se evaporan. El aceite amarillo residual (3.04 gramos) se purifica mediante cromatografía (gel de sílice 60, malla 0.063-0.2, ciclohexano/acetato de etilo, 1:1).

Rendimiento: 1.08 gramos (51.2 por ciento) de un sólido incoloro. MS (EI): 211 $[M]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.77 (s, 2H), 4.1 (s, 2H), 4.11 (q, 2H), 3.82 (m, 2H), 2.70 (m, 2H), 1.22 (t 3H).

(2) Etiléster del ácido (8RS,8aSR)-4-oxo-hexahidro-pirrolo[2,1-c][1,4]oxazin-8-carboxílico) (racemato) (69)

Una solución del 68 (1.056 gramos, 5.0 milimoles) en 25 mililitros de ácido acético, se hidrogena sobre 1.056 gramos de dióxido de platino a temperatura ambiente y a presión normal durante 18 horas. La suspensión negra se diluye con 20 mililitros de DCM, y se filtra a través de un cojín de Celite. El filtrado se evapora para dar 1.09 gramos de un aceite amarillo, el cual se purifica mediante cromatografía (gel de sílice 60, malla 0.063-0.2, acetato de etilo/etanol, 9:1).

Rendimiento: 809 miligramos (75.7 por ciento) de un aceite amarillo.

323

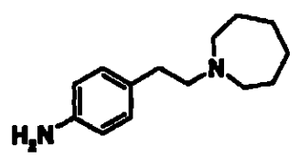
MS (ESI): 214 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.15-3.80 (m, 6H), 3.70-3.05 (m, 4H), 2.70-1.90 (m, 2H), 1.18 (t, 3H).

(3) (8RS,8aSR)-1-(hexahidro-pirrolo[2,1-c][1,4]oxazin-8-il)-metanol (racemato) (67)

A una solución del 69 (1.1 gramos, 5.0 milimoles) en 50 mililitros de tetrahidrofurano anhidro, se le agrega LAH (400 miligramos, 10 milimoles), y la mezcla se pone a reflujo durante 18 horas. La mezcla se enfría a 0°C, y se trata sucesivamente con 0.4 mililitros de agua, 0.4 mililitros de hidróxido de sodio acuoso 3N, y 1.2 mililitros de agua. La mezcla se agita durante 15 minutos, y luego se extrae tres veces con DCM. Las fases orgánicas combinadas se secan sobre sulfato de sodio anhidro y se evaporan. El aceite amarillo residual (880 miligramos) se purifica mediante cromatografía (gel de sílice 60, malla 0.063-0.2, DCM/MeOH/amoniaco concentrado, 90:9:1).

Rendimiento: 552 miligramos (70.2 por ciento) de un aceite rosado. MS (ESI): 158 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.42 (br s, 1H), 3.85 (m, 1H), 3.65 (m, 1H), 3.35 (m, 2H), 3.15 (m, 1H), 2.95 (m, 1H), 2.85 (m, 1H), 2.15-1.90 (m, 5H), 1.75 (m, 1H), 1.20 (m, 1H).

<u>Síntesis de diclorhidrato de 4-(2-azepan-1-il-etil)-fenilamina (70):</u>



(1) 1-[2-(4-nitro-fenil)-etil]-azepano (71)

Se agrega 1-(2-bromo-etil)-4-nitro-benceno (10 gramos, 43.47 milimoles) bajo argón, a una mezcla de azepano (4.9 mililitros, 43.47 milimoles) y carbonato de potasio (6 gramos, 43.47 milimoles) en 100 mililitros de N,N-dimetilformamida. Después de agitar durante la noche a temperatura ambiente, la mezcla se filtra y se evapora bajo un alto vacío. El residuo se disuelve en acetato de etilo, se lava con agua y salmuera, y se seca sobre sulfato de sodio. La evaporación dio 9.1 gramos (84 por ciento) de un aceite amarillo.

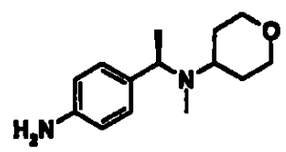
MS (ESI): 247.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 8.15 (d, 2H), 7.55 (d, 2H), 2.87 (t, 2H), 2.73 (t, 2H), 2.65 (t, 4H), 1.5-1.6 (m, 8H).

(2) Diclorhidrato 4-(2-azepan-1-il-etil)-fenilamina (70)

El compuesto 71 (9.1 gramos, 36.65 milimoles) se hidrogena durante 3 horas a temperatura ambiente con paladio sobre carbono en 150 mililitros de etanol y 18.3 mililitros de ácido clorhídrico acuoso 4M. La mezcla se filtra sobre Celite, y se evapora.

Rendimiento: 10.7 gramos (100 por ciento) de un sólido beige. MS (ESI): 219 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 10.85 (br, 1H), 9.8 (br, 3H), 7.3 (m, 2H), 7.2 (m, 2H), 3.42 (m, 2H), 3.25 (m, 2H), 3.18 (m, 2H), 3.08 (m, 2H), 1.85 (m, 4H), 1.68 (m, 2H), 1.58 (m, 2H).

<u>Síntesis de diclorhidrato [(R)-1-(4-amino-fenil)-etil]-metil-(tetrahidro-piran-4-il)-amina (72) (esquema de reacción 11):</u>



(1) Metil-[(R)-1-(4-nitro-fenil)-etil]-(tetrahidr -piran-4-il)-amina

325

(73)

Se disuelven clorhidrato de (R)-α-metil-4-nitro-bencil-amonio (Aldrich, 3 gramos, 15 milimoles), tetrahidropiridona (1.5 gramos, 15 milimoles), piridina (1.2 mililitros, 15 milimoles) en 100 mililitros de DCE. Se agrega triacetoxiborohidruro de sodio (4 gramos, 19 milimoles, 95 por ciento) con agitación a temperatura ambiente; después de 18 horas de tiempo de reacción, se agrega formaldehído (2.4 mililitros, 30 por ciento en agua), seguido por triacetoxiborohidruro de sodio (3 gramos, 14 milimoles, 95 por ciento), y la mezcla se agita nuevamente durante 18 horas a temperatura ambiente. Después de la adición de HCl 2M, el producto se aísla mediante distribución entre amoniaco acuoso y EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan bajo presión reducida. El producto crudo (3.2 gramos, 82 por ciento) se utiliza sin mayor purificación.

MS (ESI): 265 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 8.20 (d, 2H), 7.55 (d, 2H), 4.0 (br m, 2H), 3.95 (br m, 1H), 3.3 (br m, 2H), 2.7 (br m, 1H), 2.20 (s, 3H), 1.7 (br m, 4H), 1.40 (d, 3H).

(2) Diclorhidrato de [(R)-1-(4-amino-fenil)-etil]-metil-(tetrahidro-piran-4-il)-amina (72)

La metil-[(R)-1-(4-nitro-fenil)-etil]-(tetrahidro-piran-4-il)-amina 73 anterior (3.2 gramos, 12 milimoles) se agita con RaNi (1 gramo) en 100 mililitros de MeOH. Se agrega por goteo monohidrato de hidrazina (3.2 mililitros) a temperatura ambiente, y la mezcla de

326

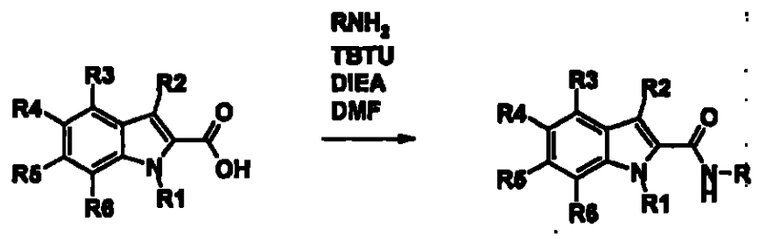
reacción se agita durante 3 horas adicionales. Después de la filtración y de la evaporación bajo presión reducida, se aísla el producto mediante distribución entre Et_2O y salmuera, secado de la fase orgánica con sulfato de sodio, filtración, y evaporación, como un aceite amarillo (2.6 gramos, 92 por ciento).

MS (ESI): 235 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 7.15 (d, 2H), 6.65 (d, 2H), 4.0 (br m, 2H), 3.7 (br m, 1H), 3.6 (NH2), 3.3 (br m, 2H), 2.7 (r m, 1H), 2.20 (s, 3H), 1.7 (br m, 4H), 1.30 (d, 3H).

Síntesis de las indol-2-carboxamidas

Las indol-2-carboxamidas se preparan en general mediante un acoplamiento mediado por TBTU de los ácidos indol-2-carboxílicos apropiadamente sustituidos con las aminas correspondientes en la presencia de base Hunig (Esquema de Reacción 12).

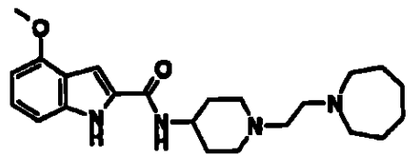
Esquema de Reacción 12:



En seguida se da un ejemplo ilustrativo.

Ejemplo 1

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-1H-indol-2-carboxílico.



327

Una solución del ácido 4-metoxi-1H-indol-2-carboxílico (930 miligramos, 4.86 milimoles), la amina 5 (1.63 gramos, 4.86 milimoles), y DIEA (2.5 mililitros, 14.58 milimoles) en 20 mililitros de N,N-dimetilformamida, se trata con TBTU sólido (1.56 gramos, 4.86 milimoles). La mezcla se agita durante la noche, y luego se evapora. El residuo crudo se disuelve en EtOAc, y se lava dos veces con dicarbonato de sodio (10 por ciento). Las capas acuosas se vuelven a extraer con DCM, las capas orgánicas combinadas se lavan con salmuera y se secan con sulfato de sodio. Luego se purifica el producto crudo mediante cromatografía sobre gel de sílice utilizando DCM (saturada con amoniaco) y MeOH (del 0 por ciento al 2 por ciento).

Rendimiento: 0.975 gramos (50 por ciento) de un polvo beige.

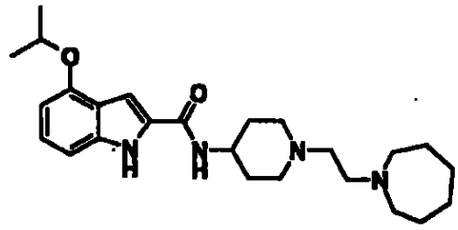
MS (ESI) 399.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.24 (d, 1H), 7.28 (s, 1H), 7.9 (t, 1H), 7.0 (d, 1H), 6.5 (d, 1H), 3.75-3.9 (m, 4H), 2.92-3.25 (m, 8H), 2.73 (m, 2H), 2.2 (m, 2), 1.52-1.9 (m, 12H).

La formación de los diclorhidratos se puede lograr mediante el tratamiento de una solución de la base libre en DCM o acetona con HCl 2M en éter a 0°C.

Ejemplo 2

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isopropoxi-1H-indol-2-carboxílico

328



Este compuesto se sintetiza de una manera análoga al Ejemplo 1 a partir del ácido 4-isopropoxi-1H-indol-2-carboxílico 74 (para la preparación, ver más adelante) y la amina 5.

MS (ESI): 427.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.24 (d, 1H), 7.22 (d, 1H), 7.06 (t, 1H), 6.98 (d, 1H), 6.51 (d, 1H), 4.75 (m, 1H), 3.75 (m, 1H), 2.99 (m, 2H), 253-2.64 (m, 6H), 2.39 (m, 2H), 2.02 (m, 2H), 1.77 (m, 2H), 1.49-163 (m, 10H), 1.35 (d, 6H).

Síntesis del ácido 4-isopropoxi-1H-indol-2-carboxílico (74):

(1) Paso A: Metiléster del ácido 4-hidroxi-1H-indol-2-carboxílico (75)

A una solución helada del metiléster del ácido 4-metiloxi-1H-indol-2-carboxílico (1 gramo, 4.87 milimoles) en DCM (10 mililitros), se le agrega BBr3 (1M en DCM, 4.9 mililitros, 4.9 milimoles). Se agita durante 1 hora, y se agrega otro equivalente (4.9 mililitros) de BBr3. Después de otra hora, la mezcla se vierte sobre hielo, y se ajusta el pH a 7 con bicarbonato de sodio. La extracción con DCM dio un polvo amarillo.

Rendimiento: 0.82 gramos (88 por ciento), MS (ESI): 192.0 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.78 (br s, 1H), 9.73 (s, 1H), 7.21 (d, 1H), 7.05 (dd, 1H), 6.89 (d, 1H), 6.4 (d, 1H), 3.86 (s, 3H).

329

(2) Pas B: Metiléster del ácido 4-isopropoxi-1H-indol-2-carboxílico (76)

Se agrega lentamente DEAD (0.227 mililitros, 1.47 milimoles) a una solución de metiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 75 (200 miligramos, 105 milimoles), trifenilfosfina (384 miligramos, 1.47 milimoles), e isopropanol (0.108 mililitros, 1.43 milimoles) en 2 mililitros de tetrahidrofurano. La agitación se continúa durante 20 minutos, y luego se evapora el solvente. La mezcla cruda se purifica mediante cromatografía sobre gel de sílice utilizando ciclohexano/EtOAc (9/1).

Rendimiento: 89 miligramos (37 por ciento). MS (ESI): 234.0 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.89 (s, 1H), 7.26 (t, 1H), 7.70 (s, 1H), 6.98 (d, 1H), 6.54 (d, 1H), 4.72 (m, 1H), 3.85 (s, 3H), 1.33 (d, 6H).

(3) Paso C: Ácido 4-isopropoxi-1H-indol-2-carboxílico (74)

El metiléster del ácido 4-isopropoxi-1H-indol-2-carboxílico 76 (114 miligramos, 0.49 milimoles) se disuelve en 5 mililitros de tetrahidrofurano. Se agrega una solución 2M de LiOH en agua (2.5 mililitros, 5 milimoles), y la mezcla se agita durante 48 horas. Luego se evapora el solvente, y el residuo se divide entre agua y EtOAc. La capa de agua se acidifica con HCl, y se extrae dos veces con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se seca sobre sulfato de sodio anhidro, se filtran y se evaporan para dar un polvo amarillo.

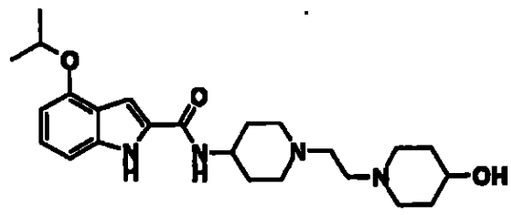
Rendimiento: 95 miligramos (89 por ciento). MS (ESI): 219.9 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.72 (br s, 1H), 7.14 (dd, 1H), 7.0 (m,

330
231

2H), 6.55 (d, 1H), 4.72 (m, 1H), 1.33 (d, 6H).

Ejemplo 36b

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isopropoxi-1H-indol-2-carboxílico

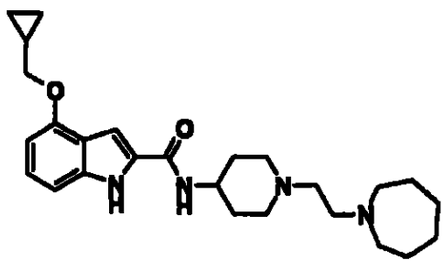


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isopropoxi-1H-indol-2-carboxílico 74 (para la preparación, ver el Ejemplo 2), y la amina 21.

MS (ESI): 429.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.42 (s, 1H), 8.2 (d, 1H), 7.19 (s, 1H), 7.02 (t, 1H), 6.94 (d, 1H), 6.48 (d, 1H), 4.72 (m, 1H), 45 (br s, 1H), 3.74 (m, 1H), 3.25-345 (m, 3H), 2.86 (m, 2H), 2.71 (m, 2H), 2.37 (r s, 4H), 2.0 (m, 4H), 1.73 (m, 4H), 1.54 (m, 2H), 1.33 (d, 6H).

Ejemplo 4

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo

331

1, a partir del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico 77 (para la preparación, ver más adelante), y la amina 5.

MS (ESI): 439.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.96 (d, 1H), 6.42 (d, 1H), 3.9 (d, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.47-1.63 (m, 10H), 1.3 (m, 1H), 0.61 (m, 2H), 0.3 (m, 2H).

Síntesis del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico (77):

(1) **Paso A: Ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico (78)**

Se agrega lentamente DEAD (2.1 mililitros, 13.65 milimoles) a una solución de etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 79 (2 gramos, 9.75 milimoles), trifenilfosfina (3.58 gramos, 13.65 milimoles), y ciclopropil-metanol (1.05 mililitros, 12.26 milimoles) en 20 mililitros de tetrahidrofurano, de tal manera que la temperatura siempre permanezca debajo de 30°C. La agitación se continúa durante 2 horas, y luego se evapora el solvente. El residuo crudo se purifica mediante cromatografía (ciclohexano:EtOAc/95:5. Rendimiento: 1.17 gramos (46 por ciento).

MS (ESI): 260.1 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 8.85 (s, 1H), 7.4 (s, 1H), 7.19 (t, 1H), 6.99 (d, 1H), 6.45 (d, 1H), 4.4 (q, 2H), 3.95 (d, 2H), 1.41 (t, 3H), 1.34 (m, 1H), 0.66 (m, 2H), 0.4 (m, 2H).

(2) **Paso B: Ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico (77)**

332

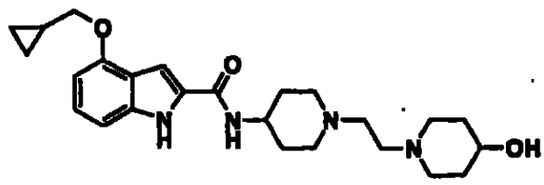
El etiléster del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 78 obtenido anteriormente, se mezcla con una solución 2M de KOH en EtOH (16.9 mililitros, 33.8 milimoles), y se agita durante 24 horas. Luego se evapora el solvente, y el residuo se divide entre agua y DCM. La capa de agua se acidifica con HCl, y se extrae dos veces con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan para dar un polvo blanco.

Rendimiento: 1.02 gramos (99 por ciento).

MS (ESI): 232.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 8.84 (s, 1H), 7.55 (s, 1H), 7.26 (t, 1H), 7.01 (d, 1H), 6.48 (d, 1H), 3.97 (d, 2H), 1.36 (m, 1H), 0.66 (m, 2H), 0.41 (m, 2H).

Ejemplo 5

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico



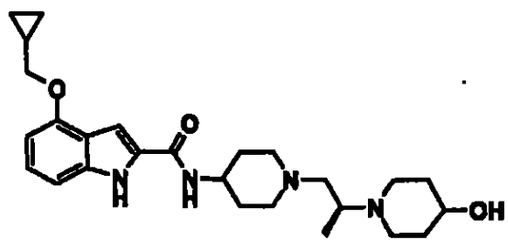
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico 77 (para la preparación, ver el Ejemplo 4), y la amina 21.

MS (ESI): 441.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.96 (d, 1H), 6.42 (d, 1H), 4.49 (d, 1H), 3.91 (d, 2H), 3.72 (m, 1H), 3.4 (m, 1H), 2.86 (m, 2H), 2.71

(m, 2H), 2.38 (br s, 4H), 1.99 (m, 4H), 1.75 (m, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 1.22-1.42 (m, 3H), 0.61 (m, 2H), 0.37 (m, 2H).

Ejemplo 6

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico



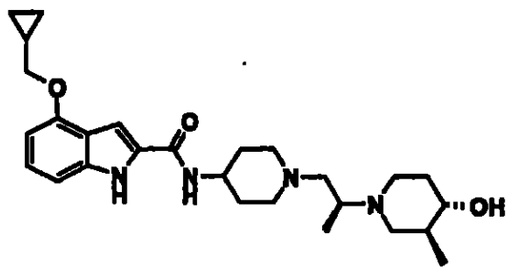
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico 77 (ver el Ejemplo 4) y la amina 50.

MS (ESI): 455.4 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 7.14 (s, 1H), 6.98 (t, 1H), 6.89 (d, 1H), 6.33 (d, 1H), 3.83 (d, 2H), 3.75 (m, 1H), 3.45 (m, 1H), 2.93 (m, 1H), 2.77 (m, 1H), 2.68 (m, 3H), 2.39 (m, 1H), 2.26 (m, 2H), 211 (m, 2H), 1.95 (m, 1H), 1.79 (m, 2H), 1.73 (m, 2H), 1.55 (m, 2H), 1.42 (m, 2H), 1.21 (m, 1H), 0.93 (d, 3H), 0.51 (m, 2H), 0.28 (m, 2H).

Ejemplo 7

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico

334

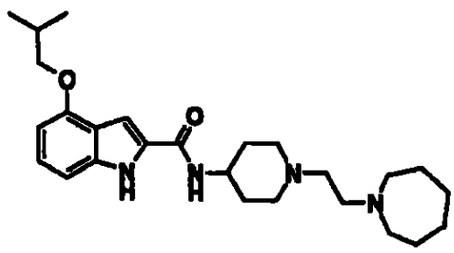


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico 77 (ver el Ejemplo 4), y la amina 56.

MS (ESI): 469.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.2 (d, 1H), 7.27 (s, 1H), 7.01 (t, 1H), 6.95 (d, 1H), 6.41 (d, 1H), 444 (d, 1H), 3.91 (d, 2H), 3.74 (m, 1H), 2.61-2.95 (m, 6H), 2.04-2.38 (m, 4H), 1.85-1.97 (m, 2H), 1.66-1.81 (m, 3H), 1.45-1.63 (m, 2H), 1.2-1.43 (m, 3H), 0.91 (d, 3H), 0.87 (d, 3H), 0.61 (m, 2H), 0.37 (m, 2H).

Ejemplo 8

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver más adelante), y la amina 5.

335
330

MS (ESI): 441.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (d, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.46 (d, 1H), 3.84 (d, 2H), 3.75 (m, 1H), 2.99 (m, 1H), 2.53-267 (m, 6H), 2.41 (m, 2H), 2.1 (m, 1H), 2.02 (m, 2H), 1.78 (m, 2H), 1.48-1.62 (m, 8H), 1.06 (d, 6H).

Síntesis del ácido 4-Iobutoxi-1H-Indol-2-carboxílico (80):

(1) Paso A: Etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico (79)

A una solución del ácido 4-benciloxi-1H-indol-2-carboxílico (29 gramos, 98.2 milimoles) en una mezcla de MeOH (750 mililitros) y DCM (500 mililitros), se le agrega 1 gramo de Pd/C (10 por ciento). Se hidrogena bajo presión normal durante 24 horas. Después de la filtración y la evaporación, se obtiene un polvo blanco.

Rendimiento: 19.63 (97 por ciento). MS (ESI): 206.0 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.72 (br s, 1H), 9.69 (s, 1H), 7.2 (s, 1H), 7.05 (t, 1H), 6.98 (d, 1H), 6.38 (d, 1H), 4.33 (q, 2H), 1.32 (t, 3H).

(2) Paso B: Etiléster del ácido 4-Isobutoxi-1H-indol-2-carboxílico (81)

Se agrega lentamente DEAD (10.2 mililitros, 65.28 milimoles) a una solución de etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 79 (9.57 gramos, 46.63 milimoles), trifenilfosfina (17.12 gramos, 65.28 milimoles), e isobutanol (5.9 mililitros, 63.42 milimoles) en 100 mililitros de tetrahidrofurano, de tal manera que la temperatura siempre permanezca debajo de 30°C. La agitación se continúa durante 3 horas, y luego se evapora el solvente. La mezcla cruda se

purifica mediante cromatografía sobre gel de sílice, utilizando primero ciclohexano como eluyente, y luego cantidades crecientes de EtOAc (desde el 5 por ciento hasta el 50 por ciento).

Rendimiento: 8 gramos (65 por ciento).

MS (ESI): 260.0 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.86 (s, 1H), 7.36 (s, 1H), 7.22 (t, 1H), 6.99 (d, 1H), 6.48 (d, 1H), 4.4 (q, 2H), 3.86 (d, 2H), 2.2 (m, 1H), 1.42 (t, 3H), 1.09 (d, 6H).

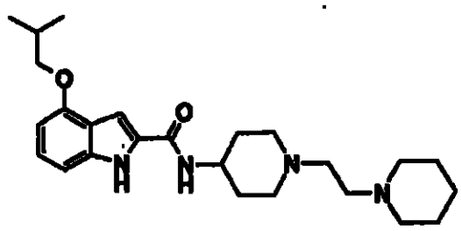
(3) Paso C: Ácido 4-Isobutoxi-1H-indol-2-carboxílico (80)

Se mezcla el etiléster del ácido 4-isobutoxi-1H-indol-2-carboxílico 81 (5.2 gramos, 19.9 milimoles) con una solución 1M de KOH en EtOH (99.5 mililitros, 99.5 milimoles) y se agita durante 24 horas. Luego se evapora el solvente, y el residuo se divide entre agua y éter. La capa de agua se acidifica con HCl, y se extrae dos veces con éter. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan para dar un polvo beige.

Rendimiento: 4.32 gramos (93 por ciento). MS (ESI): 2342 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.74 (br s, 1H), 7.13 (dd, 1H), 7.06 (s, 1H), 7.0 (d, 1H), 6.49 (d, 1H), 3.85 (d, 2H), 3.35 (br s, 1H), 2.1 (m, 1H), 1.03 (d, 6H).

Ejemplo 9

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico

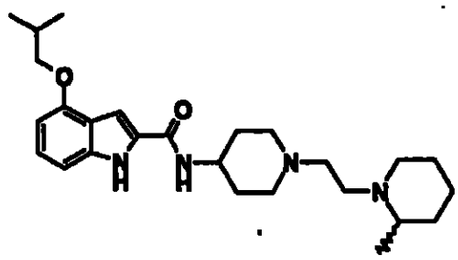


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 1.

MS (ESI): 427.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (d, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 3.84 (d, 2H), 3.75 (m, 1H), 2.88 (m, 2H), 2.38 (m, 8H), 2.1 (m, 1H), 2.02 (m, 2H), 1.78 (m, 2H), 1.32-1.63 (m, 9H), 1.07 (d, 6H).

Ejemplo 10

{1-[2-(RS)-2-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 10.

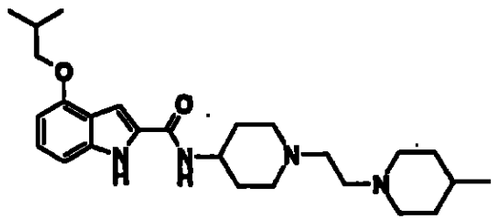
MS (ESI): 441.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (d, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H),

338

3.85 (d, 2H), 3.75 (m, 1H), 2.65-2.93 (m, 7H), 2.05-2.43 (m, 5H), 2.01 (m, 2), 1.78 (m, 2H), 1.1-1.62 (m, 6H), 1.06 (d, 6H), 1.01 (d, 3H).

Ejemplo 11

{1-[2-(4-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico

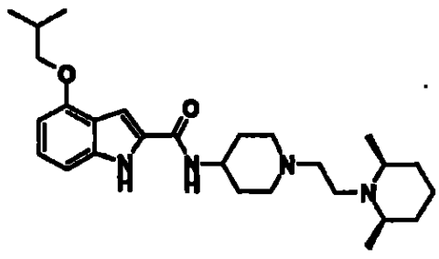


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 7.

MS (ESI): 441.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.2 (d, 1H), 7.22 (d, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 6.86 (d, 2H), 3.75 (m, 1H), 2.86 (m, 4H), 2.4 (br s, 4H), 2.11 (m, 1H), 2.02 (m, 2H), 1.9 (m, 2H), 1.79 (m, 2H), 1.55 (m, 4H), 1.3 (m, 1H), 1.11 (m, 2H), 1.06 (d, 6H), 0.88 (d, 3H).

Ejemplo 12

{1-[2-(2,6-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



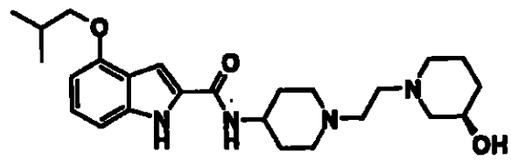
339

Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 27.

MS (ESI): 455.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.2 (d, 1H), 7.2 (d, 1H), 7.04 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 3.85 (d, 2H), 3.75 (m, 1H), 2.87 (m, 2H), 2.7 (m, 2H), 2.43 (m, 2H), 2.32 (m, 2H), 2.1 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.45-1.65 (m, 5H), 1.0-1.35 (m, 16H).

Ejemplo 13

{1-[2-((R)-3-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 12.

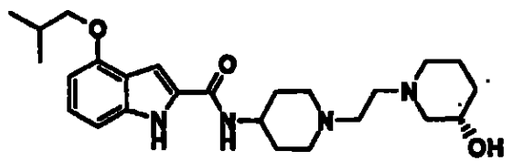
MS (ESI): 443.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.23 (s, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.54 (d, 1H), 3.84 (d, 1H), 3.75 (m, 1H), 3.42 (m, 1H), 2.62-2.93 (m, 2H), 2.49 (br s, 4H), 2.1 (m, 1H), 2.0 (m, 2H), 1.3-1.9 (m, 11H), 1.06 (d, 6H).

Ejemplo 14

{1-[2-((S)-3-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del

340

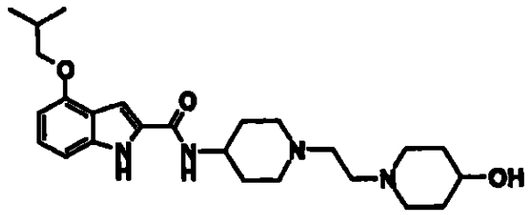
ácido 4-is butoxi-1H-indol-2-carb xílico



Este compuesto se obtiene mediante separación de preparación del material racémico utilizando una fase estacionaria quiral de HPLC (CHIRALCEL OJ-H 1170). La estereoquímica absoluta se asigna mediante una comparación con el isómero-(R) enantioméricamente definido de Ejemplo 13.

Ejemplo 15

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



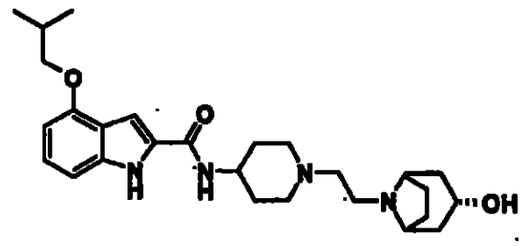
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 21.

MS (ESI): 443.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H), 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

341

Ejemplo 16

{1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico

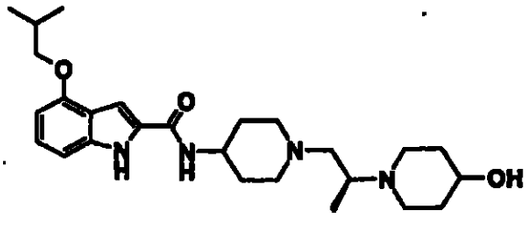


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 24.

MS (ESI): 469.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.23 (d, 1H), 7.72 (s, 1H), 6.9-7.1 (m, 2H), 6.46 (d, 1H), 4.57 (br s, 1H), 3.85 (d, 2H), 3.77 (m, 1H), 3.2-3.7 (br m, 4H), 2.94 (m, 2H), 2.75 (m, 2H), 2.56 (m, 2H), 1.5-2.25 (m, 15H), 1.06 (d, 6H).

Ejemplo 17

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (ver el

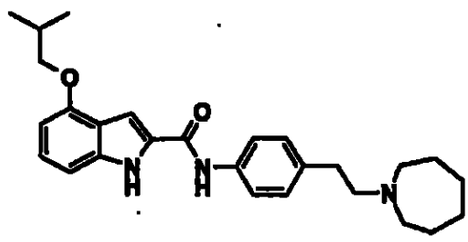
342

Ejemplo 8), y la amina 50.

MS (ESI): 457.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (d, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 644 (d, 1H), 4.47 (d, 1H), 3.84 (d, 2H), 3.73 (m, 1H), 3.37 (m, 1H), 2.6-2.95 (m, 5H), 2.05-2.38 (m, 6H), 1.92 (m, 1H), 1.76 (m, 2H), 1.69 (m, 2H), 1.2-1.65 (m, 4H), 1.05 (d, 6H), 0.92 (d, 3H).

Ejemplo 18

[4-(2-azepan-1-il-etil)-fenil]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



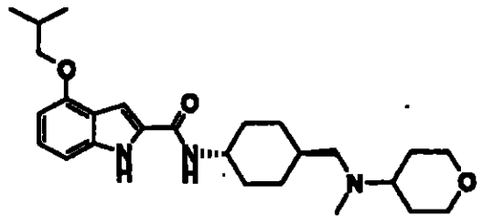
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 70.

MS (ESI): 434.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 10.07 (s, 1H), 7.67 (d, 2H), 7.48 (d, 1H), 7.18 (d, 2H), 7.08 (t, 1H), 7.01 (d, 1H), 6.49 (d, 1H), 3.88 (d, 2H), 257-2.62 (m, 8H), 2.13 (m, 2H), 1.48-1.63 (m, 8H), 1.08 (d, 6H).

Ejemplo 19

(4-{[metil-(tetrahidro-piran-4-il)-amino]-metil}-ciclohexil)-amida del ácido 4-isobut xi-1H-indol-2-carboxílic

343

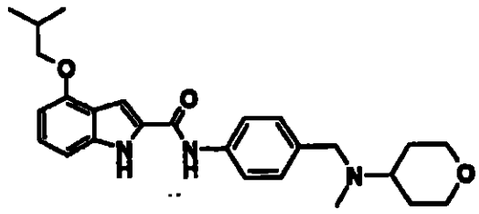


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y trans-4-amino-ciclohexilmetil)-metil-(tetrahidro-piran-4-il)-amina (Publicación Internacional No. WO2000/68203).

MS (ESI): 442.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.18 (d, 1H), 7.23 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 3.82-3.93 (m, 4H), 3.74 (m, 1H, 3.22-3.31 (m, 2H), 2.7 (s, 3H), 2.45 (m, 1H), 2.18 (m, 4H), 2.11 (m, 1H), 1.85 (m, 4H), 1.6 (m, 2H), 1.2-1.48 (m, 5H), 1.06 (d, 6H).

Ejemplo 20

(4-{[metil-(tetrahidro-piran-4-il)-amino]-metil}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



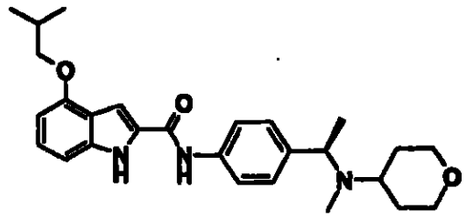
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y (4-amino-bencil)-metil-

(tetrahidropiran-4-il)-amina (Publicación Internacional No. WO 99/32468).

MS (ESI): 436.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 10.12 (s, 1H), 7.74 (d, 2H), 7.5 (s, 1H), 7.27 (d, 2H), 7.09 (t, 1H), 7.02 (d, 1H), 6.5 (d, 1H), 3.84-3.94 (m, 4H), 3.52 (s, 2H), 3.22-3.32 (m, 2H), 2.6 (m, 1H), 2.08-2.2 (m, 4H), 1.72 (m, 2H), 1.53 (m, 2H), 1.07 (d, 6H).

Ejemplo 21

(4-{(R)-1-[metil-(tetrahidro-piran-4-il)-amino]-etil}-fenil)-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico



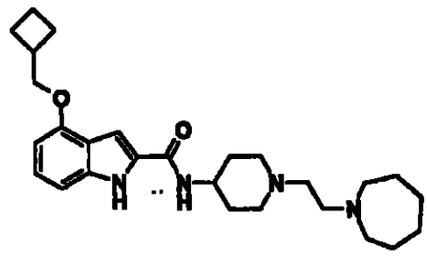
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8), y la amina 72.

MS (ESI): 450.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.66 (s, 1H), 10.12 (s, 1H), 7.73 (d, 2H), 7.5 (d, 1H), 7.3 (d, 2H), 7.09 (t, 1H), 7.02 (d, 1H), 6.5 (d, 1H), 3.76-3.91 (m, 5H), 3.1-3.33 (m, 2H), 2.68 (m, 1H), 2.04-2.2 (m, 4H), 1.36-1.68 (m, 4H), 1.28 (d, 3H), 1.08 (d, 6H).

Ejemplo 22

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-ciclobutilmet xi-1H-indol-2-carboxílico

345



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 82 (para la preparación, ver más adelante), y la amina 5.

MS (ESI): 453.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.05 (d, 2H), 3.74 (m, 1H), 2.86 (m, 2H), 2.78 (m, 1H), 255-2.7 (m, 6H), 2.4 (m, 2H), 1.83-2.18 (m, 8H), 1.76 (m, 2H), 1.47-1.63 (m, 10H).

Síntesis de 4-ciclobutilmetoxi-1H-indol-2-carboxílico (82):

(1) Paso A: Ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico (83)

Se agrega lentamente DEAD (21 mililitros, 13.65 milimoles) a una solución de etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 79 (2 gramos, 9.75 milimoles), trifenilfosfina (3.58 gramos, 13.65 milimoles), y ciclobutil-metanol (1.25 mililitros, 12.26 milimoles) en 20 mililitros de tetrahidrofurano, de tal manera que la temperatura siempre permanezca debajo de 30°C. La agitación se continúa durante 2 horas, y luego se evapora el solvente. El residuo crudo se purifica mediante cromatografía (ciclohexano:EtOAc(95:5).

Rendimiento: 1.86 gramos (70 por ciento). MS (ESI): 274.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 8.83 (, 1H), 7.35 (s, 1H), 7.21 (t, 1H), 6.98

346

(d, 1H), 6.49 (d, 1H), 4.4 (2, 2H), 4.07 (d, 2H), 2.85 (m, 1H), 217 (m, 2H), 1.95 (m, 4H), 1.42 (t, 3H).

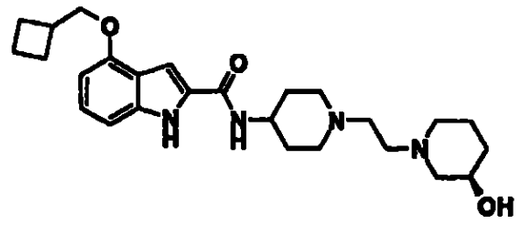
(2) Paso B: Ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico (82)

El etiléster del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 83 obtenido anteriormente, se mezcla con una solución 2M de KOH en EtOH (16.9 mililitros, 33.8 milimoles), y se agita durante 24 horas. Luego se evapora el solvente, y el residuo se divide entre agua y DCM. La capa de agua se acidifica con HCl, y se extrae dos veces con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan, para dar un polvo blanco.

Rendimiento: 1.65 gramos (99 por ciento). MS (ESI) 246.3 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 11.74 (br s, 1H), 714 (t, 1H), 7.03 (s, 1H), 6.99 (d, 1H), 6.51 (d, 1H), 4.05 (d, 2H), 28 (m, 1H), 2.11 (m, 2H), 1.93 (m, 4H).

Ejemplo 23

{1-[2-(3-(R)-hidroxi-piperidin-1-il)-etil]-piperidin-4-}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 82 (para

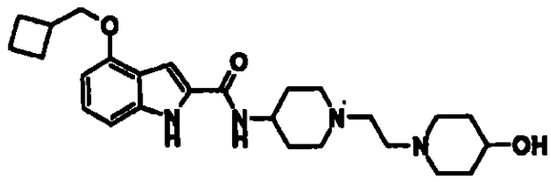
347

la preparación, ver el Ejemplo 22), y la amina 12.

MS (ESI): 455.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.22 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.47 (d, 1H), 4.56 (br s, 1H), 4.05 (d, 2H), 3.75 (m, 1H), 3.43 (m, 1H), 2.88 (m, 3H), 2.78 (m, 1H), 2.68 (m, 1H), 2.42 (br s, 1H), 1.83-2.2 (m, 8H), 177 (m, 4H), 1.56 (m, 4H), 1.38 (m, 2H).

Ejemplo 24

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico

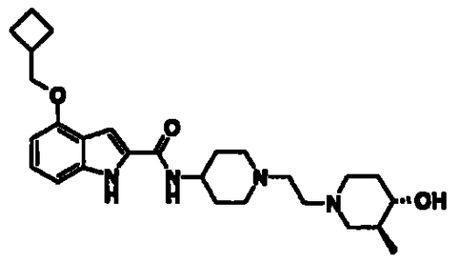


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 82 (para la preparación, ver el Ejemplo 22), y la amina 21.

MS (ESI): 455.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.49 (s, 1H), 4.05 (d, 2H), 3.73 (m, 1H), 3.41 (m, 1H), 2.87 (m, 2H), 2.78 (m, 1H), 2.7 (m, 2H), 2.38 (m, 4H), 2.14 (m, 2H), 1.83-2.07 (m, 8H), 1.76 (m, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 1.35 (m, 2H).

Ejemplo 25

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico

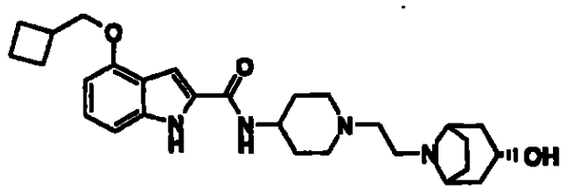


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 82 (ver el Ejemplo 22), y la amina 14.

MS (ESI): 469.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 4.48 (d, 1H), 4.04 (d, 2H), 3.73 (br m, 1H), 2.64-2.97 (m, 6H), 2.37 (m, 4H), 2.05-2.2 (m, 2H), 1.81-2.05 (m, 7H), 1.65-1.81 (m, 3H), 1.46-165 (m, 3H), 127-1.46 (m, 2H), 0.86 (d, 3H).

Ejemplo 26

{1-[2-(3-(R)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 82 (para la preparación, ver el Ejemplo 22), y la amina 24.

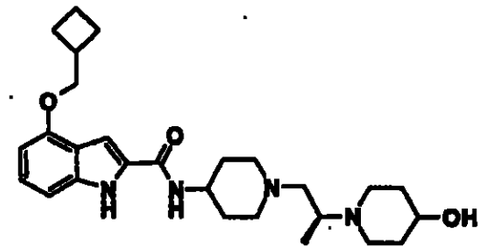
MS (ESI): 481.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.21 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H),

349

4.31 (br s, 1H), 4.04 (d, 2), 3.8 (br s, 1H), 3.74 (m, 1H), 2.89 (m, 2H), 2.78 (m, 1H), 2.42 (r m, 6H), 1.7-2.2 (m, 16H), 1.56 (m, 4H).

Ejemplo 27

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil}-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico

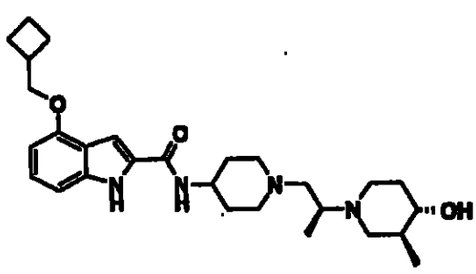


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 82 (ver el Ejemplo 22), y la amina 50.

MS (ESI): 469.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.21 (d, 1H), 7.18 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 4.46 (d, 1H), 4.05 (d, 2H), 3.74 (m, 1H), 3.36 (m, 1H), 2.6-2.95 (m, 6H), 2.04-2.4 (m, 7H), 1.83-2.0 (m, 4H), 1.64-1.81 (m, 4H), 1.45-1.63 (m, 2H), 1.23-1.42 (m, 2H), 0.92 (d, 3H).

Ejemplo 28

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico



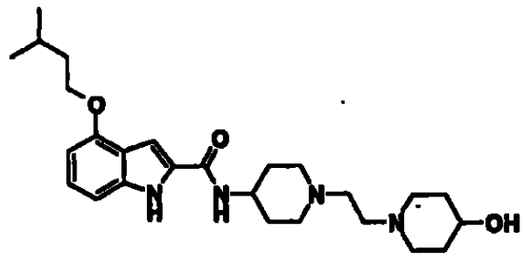
350
35

Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico 82 (ver el Ejemplo 22), y la amina 56.

MS (ESI): 483.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.22 (d, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.46 (d, 1H), 4.44 (d, 1H), 4.04 (d, 2H), 3.74 (m, 1H), 2.6-2.95 (m, 7H), 2.33 (m, 1H), 2.24 (m, 1H), 2.02-2.19 (m, 4H), 1.82-2.01 (m, 6H), 1.66-1.81 (m, 3H), 1.45-1.64 (m, 2H), 1.2-1.43 (m, 2H), 0.91 (d, 3H), 0.87 (d, 3H).

Ejemplo 29

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3-metil-butiloxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(3-metil-butiloxi)-1H-indol-2-carboxílico (84) (para la preparación, ver más adelante), y la amina 21.

Rendimiento: 110 miligramos (43 por ciento). MS (ESI): 457 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.4 (s, 1H), 10.5-10.8 (br, 2H), 8.58 (d, 1H), 7.22 (s, 1H), 7.05 (dd, 1H), 6.95 (d, 1H), 6.48 (d, 1H), 4.1 (t, 2H), 3.4-3.75 (m, 9H), 2.9-3.2 (m, 4H), 1.65-2.1 (m, 11H), 0.95 (d, 6H).

351

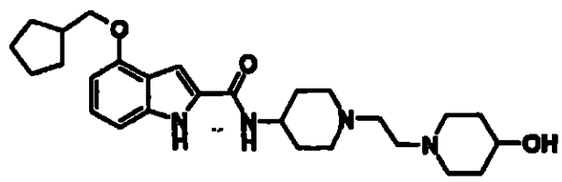
Síntesis del ácid 4-(3-metil-butiloxi)-1H-indol-2-carboxílico (84):

Este compuesto se sintetiza de una manera análoga al Ejemplo (85), a partir de 3-metil-butan-1-ol.

Rendimiento: 0.54 gramos (100 por ciento). MS (ESI): 246 $[M-H]^-$.

Ejemplo 30

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico 86 (para la preparación, ver más adelante), y la amina 21.

MS (ESI): 469.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.42 (s, 1H), 8.19 (d, 1H), 7.18 (s, 1H), 7.01 (t, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 4.48 (br. s, 1H), 3.93 (d, 2H), 3.72 (m, 1H), 3.4 (m, 1H), 3.15 (br. s, 1H) 2.86 (m, 2H), 2.7 (m, 2H), 2.37 (m, 4H), 1.99 (m, 4H), 1.25-1.88 (m, 16H).

Síntesis del ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico (86)

(1) Paso A: Etiléster del ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico (87)

Se agrega lentamente DEAD (5.3 mililitros, 34.1 milimoles) a una solución de etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 79 (2 gramos, 24.36 milimoles), trifenilfosfina (8.95 gramos, 34.1

352

milimoles) y ciclopentil-metanol (3.58 mililitros, 33.13 milimoles) en 30 mililitros de tetrahidrofurano, de tal manera que la temperatura siempre permanezca debajo de 30°C. La agitación se continúa durante 2 horas, y luego se evapora el solvente. El residuo crudo se purifica mediante cromatografía (ciclohexano:EtOAc/90:10).

Rendimiento: 3.88 gramos (55 por ciento). MS (ESI): 28.3 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 8.86 (br. s, 1H), 7.35 (s, 1H), 7.21 (t, 1H), 6.98 (d, 1H), 648 (d, 1), 4.4 (q, 2H), 3.98 (d, 2H), 2.47 (m, 1H), 1.89 (m, 2H), 1.65 (m, 4H), 1.42 (t, 3H y m traslapado, 2H).

(2) Paso B: Ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico (86)

El etiléster del ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico 87 obtenido anteriormente, se mezcla con una solución 2M de KaOH en EtOH (33.8 mililitros, 67.6 milimoles) y se agita durante 24 horas. Luego se evapora el solvente, y el residuo se divide entre agua y éter. La capa de agua se acidifica con HCl, y se extrae dos veces con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran y se evaporan para dar un polvo blanco.

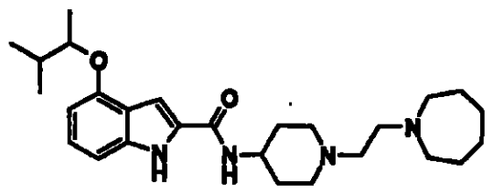
Rendimiento: 2.55 gramos (73 por ciento). MS (ESI): 260.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.73 (br. s, 1H), 7.12 (t, 1H), 7.02 (s, 1H), 6.98 (d, 1H), 6.5 (d, 1H), 3.96 (d, 2H), 2.39 (m, 1H), 1.82 (m, 2H), 1.6 (m, 4H), 14 (m, 2H).

Ejemplo 31

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácid 4-(1,2-

353

dimetil-propoxi)-1H-indol-2-carboxílic



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(1,2-dimetil-propoxi)-1H-indol-2-carboxílico 88 (para la preparación, ver más adelante), y la amina 5.

MS (ESI): 455.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.4 (s, 1H), 8.2 (d, 1H), 7.18 (d, 1H), 7.02 (dd, 1H), 6.93 (d, 1H), 6.47 (d, 1H), 4.37 (m, 1H), 3.74 (m, 1H), 2.88 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 1.89-2.06 (m, 3H), 1.75 (m, 2H), 1.46-1.62 (m, 10H), 1.24 (d, 3H), 1.0 (m, 6H).

Síntesis del ácido 4-(1,2-dimetil-propoxi)-1H-indol-2-carboxílico (88):

(1) **Paso A: Etiléster del ácido 4-(1,2-dimetil-propoxi)-1H-indol-2-carboxílico (89).**

Se agrega lentamente DEAD (5.3 mililitros, 34.1 milimoles) a una solución de etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 79 (5 gramos, 24.36 milimoles), trifenilfosfina (8.95 gramos, 34.1 milimoles), y 3-metil-butan-2-ol (3.58 mililitros, 33.13 milimoles) en 50 mililitros de tetrahidrofurano, de tal manera que la temperatura siempre permanezca debajo de 30°C. La agitación se continúa durante 3 días, y luego se evapora el solvente. La mezcla cruda se purifica mediante cromatografía sobre gel de sílice, utilizando

354

primero ciclohexano como eluyente, y luego cantidades crecientes de EtOAc (desde el 5 por ciento hasta el 50 por ciento).

Rendimiento: 2.4 gramos (36 por ciento). MS (ESI): 276.3 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 8.9 (br s, 1H), 7.35 (s, 1H), 7.2 (dd, 1H), 6.96 (d, 1H), 6.5 (d, 1H), 4.4 (q, 2H), 4.34 (t, 1H), 2.03 (m, 1H), 1.42 (t, 3H), 1.31 (d, 3H), 1.04 (m, 6H).

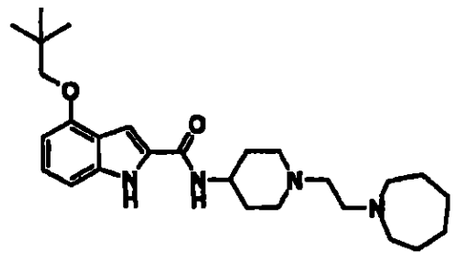
(2) Paso B: Ácido 4-(1,2-dimetil-propoxi)-1H-indol-2-carboxílico (88).

El etiléster del ácido 4-(1,2-dimetil-propoxi)-1H-indol-2-carboxílico 89 (2.4 gramos, 8.72 milimoles) se mezcla con una solución 1M de KOH en EtOH (43.6 mililitros, 87.2 milimoles), y se agita durante 48 horas. Luego se evapora el solvente, y el residuo se divide entre agua y éter. La capa de agua se acidifica con HCl, y se extrae dos veces con éter. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan, para dar un polvo beige.

Rendimiento: 2.14 gramos (99 por ciento). MS (ESI): 248.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.92 (br s, 1H), 7.52 (s, 1H), 7.27 (m, 1H), 6.99 (d, 1H), 6.51 (d, 1H), 4.34 (m, 1H), 2.02 (m, 1H), 1.33 (d, 3H), 1.04 (m, 6H).

Ejemplo 32

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico 85 (para la preparación, ver más adelante), y la amina 5.

MS (ESI): 455.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.25 (d, 1H), 7.25 (d, 1H), 7.06 (t, 1H), 6.99 (d, 1H), 6.48 (d, 1H), 3.72-3.84 (m, 3H), 2.92 (m, 1H), 2.54-2.63 (m, 6H), 2.41 (m, 2H), 2.04 (m, 2H), 1.79 (m, 2H), 1.5-1.65 (m, 1H), 1.1 (s, 9H).

Síntesis del ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico (85):

(1) Paso A: Metiléster del ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico (90)

Se agrega lentamente DEAD (0.414 mililitros, 2.66 milimoles) a una solución de metiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 75 (363 miligramos, 1.9 milimoles), trifenilfosfina (698 miligramos, 2.66 milimoles), y 2,2-dimetil-propan-1-ol (228 miligramos, 1.58 milimoles) en 8 mililitros de tetrahidrofurano. La agitación se continúa durante 20 horas, y luego se evapora el solvente. La mezcla cruda se purifica mediante cromatografía sobre gel de sílice utilizando ciclohexano/EtOAc (9/1).

Rendimiento: 271 miligramos (55 por ciento). MS (ESI): 261.9$[M+H]^+$,

356

1H-RMN ($CDCl_3$): δ (ppm) 8.9 (br s, 1H), 7.39 (s, 1H), 7.23 (dd, 1H), 7.0 (d, 1H), 6.47 (d, 1H), 3.95 (s, 3H), 3.74 (s, 2H), 1.0 (s, 9H).

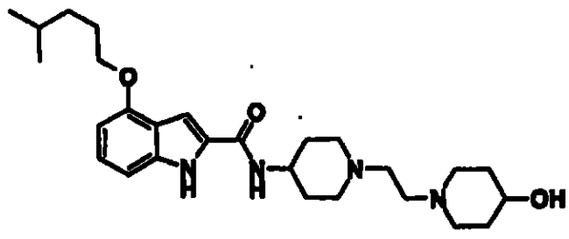
(2) Paso B: Ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico (85).

El metiléster del ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico 90 (270 miligramos, 1.03 milimoles) se disuelve en 20 mililitros de tetrahidrofurano. Se agrega una solución 2M de LiOH en agua (5.2 mililitros, 11 milimoles), y la mezcla se agita durante 48 horas. Luego se evapora el solvente, y el residuo se divide entre agua y éter. La capa de agua se acidifica con HCl, y se extrae dos veces con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan para dar un polvo amarillo.

Rendimiento: 230 miligramos 90 por ciento). MS (ESI): 248.0 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.75 (br s, 1H), 7.13 (dd, 1H), 7.08 (s, 1H), 70 (d, 1H), 6.49 (d, 1H), 4.74 (s, 2H), 1.07 (s, 9H).

Ejemplo 33

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metil-pentiloxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo

1, a partir del ácido 4-(4-metil-pentiloxi)-1H-indol-2-carboxílico (91) (para la preparación, ver más adelante), y la amina 21.

Rendimiento: 145 miligramos (70 por ciento). MS (ESI): 471 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4-10.7 (br, 2H), 8.58 (d, 1H), 7.25 (s, 1H), 7.05 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 3.95-4.2 (m, 4H), 2.95-3.8 (m, 12), 1.7-2.1 (m, 10H), 1.6 (m, 2H), 1.35 (m, 2H), 0.9 (d, 6H).

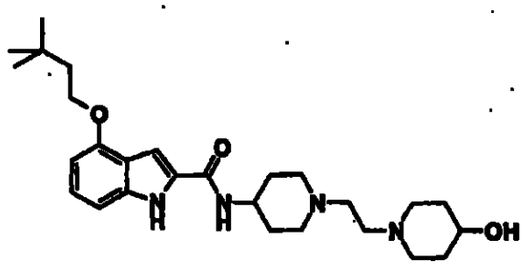
Síntesis del ácido 4-(4-metil-pentiloxi)-1H-indol-2-carboxílico (91):

Este compuesto se sintetiza de una manera análoga al (85), a partir de 4-metil-pentan-1-ol.

Rendimiento: 0.61 gramos (94 por ciento). MS (ESI): 260 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.8 (s, 1H), 11.65 (s, 1H), 7.1 (dd, 1H), 7.0 (s, 1H), 6.98 (d, 1H), 6.48 (d, 1H), 4.05 (t, 2H), 1.77 (t, 2H), 1.63 (m, 1H), 1.35 (m, 2H), 0.9 (d, 6H).

Ejemplo 34

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,3-dimetil-butoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(3,3-dimetil-butoxi)-1H-indol-2-carboxílico (92)

358

(para la preparación, ver más adelante), y la amina 21.

Rendimiento: 60 miligramos (24 por ciento). MS (ESI): 471 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.4 (s, 1H), 10.5 (br 1H) 8.58 (d, 1H), 7.17 (s, 1H), 7.0-7.1 (m, 2H), 65 (d, 1H), 4.2 (m, 2H), 4.15 (m, 1H), 3.85 (m, 1H), 3.65 (m, 4H), 31-3.5 (m, 8H), 2.0-2.2 (m, 6H), 1.75-1.85 (m, 4H), 1.03 (s, 9H).

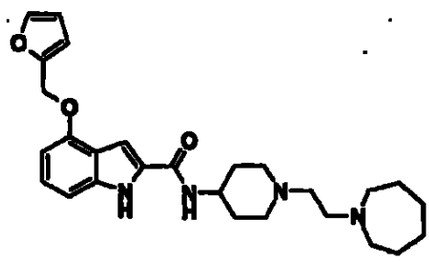
Síntesis del ácido 4-(3,3-dimetil-butoxi)-1H-indol-2-carboxílico (92):

Este compuesto se sintetiza de una manera análoga al (85), a partir de 3,3-dimetil-butan-1-ol.

Rendimiento: 1.1 gramos (100 por ciento). MS (ESI): 260 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.8 (s, 1H), 11.65 (s, 1H), 7.12 (dd, 1H), 6.98 (s, 1H), 6.95 (d, 1H), 6.52 (d, 1H), 4.13 (t, 2H), 1.75 (t, 2H), 1.0 (s, 9H).

Ejemplo 35

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(furan-2-ilmetoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(furan-2-ilmetoxi)-1H-indol-2-carboxílico 93 (para la preparación, ver más adelante), y la amina 5.

359

MS (ESI): 465.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.13 (d, 1H), 7.71 (s, 1H), 7.23 (s, 1H), 7.06 (t, 1H), 7.0 (d, 1H), 6.63 (m, 2H), 6.48 (s, 1H), 5.13 (s, 2H), 3.72 (m, 1H), 2.88 (m, 2H), 2.5-2.6 (m, 6H), 2.36 (m, 2H), 2.0 (m, 2H), 1.74 (m, 2H), 1.45-1.6 (m, 10H).

Síntesis del ácido 4-(furan-2-ilmetoxi)-1H-indol-2-carboxílico (93):

(1) Paso A: Etiléster del ácido 4-(furan-2-ilmetoxi)-1H-indol-2-carboxílico (94).

Se agrega lentamente DEAD (2.1 mililitros, 13.65 milimoles) a una solución de etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 79 (2 gramos, 9.75 milimoles), trifenilfosfina (3.58 gramos, 13.65 milimoles), y furan-2-il-metanol (1.18 mililitros, 12.26 milimoles) en 10 mililitros de tetrahidrofurano, de tal manera que la temperatura siempre permanezca debajo de 30°C. La agitación se continúa durante 2 horas, y luego se evapora el solvente. El residuo crudo se purifica mediante cromatografía (ciclohexano:EtOAc/95:5).

Rendimiento: 0.76 gramos (27 por ciento).

(2) Paso B: Ácido 4-(furan-2-ilmetoxi)-1H-indol-2-carboxílico (93).

El etiléster del ácido 4-(furan-2-ilmetoxi)-1H-indol-2-carboxílico 94 obtenido anteriormente, se mezcla con una solución 1M de KOH en EtOH (13.3 mililitros, 13.3 milimoles), y se agita durante 24 horas. Luego se evapora el solvente, y el residuo se divide entre agua y éter. La capa de agua se acidifica con HCl, y se extrae dos veces

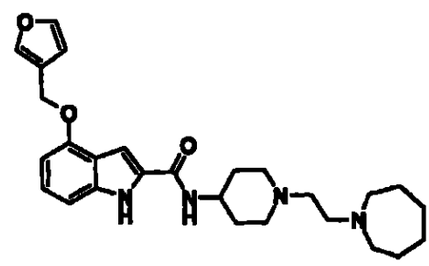
360

con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan para dar un polvo blanco.

Rendimiento: 0.329 miligramos (48 por ciento). 1H-RMN (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.73 (s, 1H), 7.69 (s, 1H), 7.14 (t, 1H), 7.02 (d, 1H), 6.98 (s, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 5.16 (s, 2H).

Ejemplo 36

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico 95 (para la preparación, ver más adelante), y la amina 5.

MS (ESI): 465.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.06 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.52-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.45-1.62 (m, 10H).

Síntesis del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico (95):

(1) Paso A: Etiléster del ácido 4-(furan-3-ilmet xi)-1H-indol-2-

361

carboxílico (96).

Se agrega lentamente DEAD (2.1 mililitros, 13.65 milimoles) a una solución de etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico 79 (2 gramos, 9.75 milimoles), trifenilfosfina (3.58 gramos, 132.65 milimoles), y furan-3-il-metanol (1.18 mililitros, 12.26 milimoles) en 10 mililitros de tetrahidrofurano, de tal manera que la temperatura siempre permanezca debajo de 30°C. La agitación se continúa durante 2 horas, y luego se evapora el solvente. El residuo crudo se tritura con éter, y el precipitado blanco se filtra. Contiene principalmente el producto. El licor madre se purifica mediante cromatografía (ciclohexano:EtOAc/95:5), y se combina con el primer precipitado. Rendimiento: 3 gramos (>100 por ciento).

(2) Paso B: Ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílic (95).

El etiléster del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico 96 obtenido anteriormente, se mezcla con una solución 1M de KOH en EtOH (35 mililitros, 35 milimoles), y se agita durante 24 horas. Luego se evapora el solvente, y el residuo se divide entre agua y éter. La capa de agua se acidifica con HCl, y se extrae dos veces con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio anhidro, se filtran, y se evaporan para un polvo blanco.

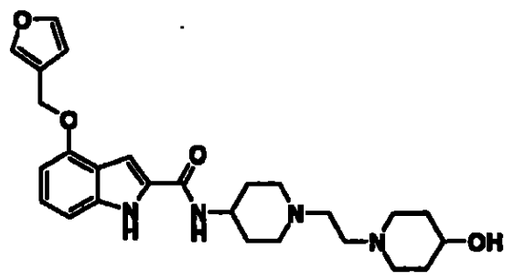
Rendimiento: 1.63 gramos (65 por ciento). MS (ESI): 258.0 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.71 (s, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 7.13 (m, 1H), 7.01 (m, 2H), 6.62 (m, 2H), 5.07 (s,

362

2H).

Ejemplo 37

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico

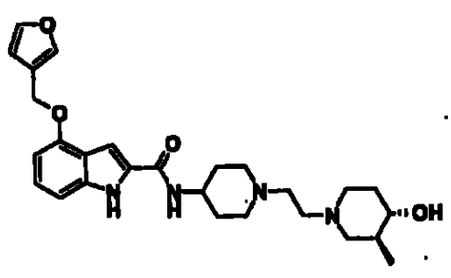


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico 95 (ver el Ejemplo 36), y la amina 21.

MS (ESI): 467 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.13 (d, 1H), 7.81 (s, 1H), 768 (t, 1H), 7.22 (d, 1H), 7.06 (t, 1H), 6.98 (d, 1H), 6.62 (s, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 4.48 (d, 1H), 3.73 (m, 1H), 3.4 (m, 1H), 2.86 (m, 2H), 2.7 (m, 2H), 2.36 (br s, 4H), 2.0 (m, 4H), 1.72 (m, 4H), 1.52 (m, 2H), 1.35 (m, 2H).

Ejemplo 38

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico



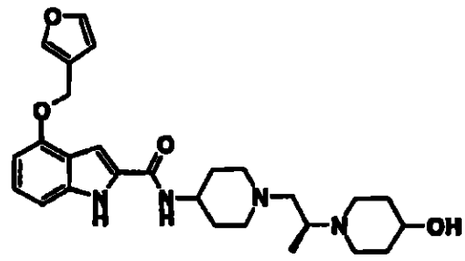
363

Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico 95 (para la preparación, ver el Ejemplo 36), y la amina 14.

MS (ESI): 481.2 $[M+H]^+$, 1H-RMN (CD_3-OD): δ (ppm) 7.63 (s, 1H), 7.51 (s, 1H), 7.23 (s, 1H), 7.13 (t, 1H), 7.04 (d, 1H), 6.6 (d, 1H), 6.57 (s, 1H), 5.08 (s, 2H), 3.9 (m, 1H), 2.83-3.12 (m, 5H), 2.55 (m, 4H), 2.21 (m, 2H), 2.11 (m, 1H), 1.84-2.0 (m, 3H), 151-1.83 (m, 5H), 0.99 (d, 3H).

Ejemplo 39

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico



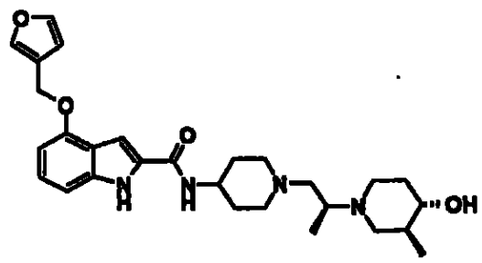
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico 95 (ver el Ejemplo 36), y la amina 50.

MS (ESI): 481.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.60 (d, 1H), 5.03 (d, 2H), 4.45 (d, 1H), 3.73 (m, 1H), 3.37 (m, 1H), 2.9 (m, 1H), 2.8 (m, 1H), 2.6-2.75 (m, 3H), 2.05-2.37 (m, 5H), 1.9 (m, 1H), 1.65-1.8 (m, 4H), 1.42-1.62 (m, 2H), 1.2-1.4 (m, 2H), 0.92 (d, 3H).

364

Ejemplo 40

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico

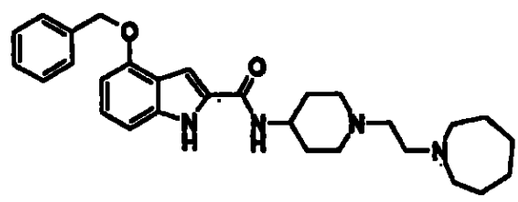


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico 95 (ver el Ejemplo 36), y la amina 56.

MS (ESI): 495.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.23 (s, 1H), 7.05 (t 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 4.43 (d, 1H), 3.72 (m, 1H), 2.58-2.94 (m, 5H), 2.32 (m, 1H), 2.24 (m, 1H), 2.03-2.19 (m, 2H), 1.84-1.96 (m, 2H), 1.66-1.79 (m, 3H), 1.42-1.62 (m, 2H), 1.2-1.41 (m, 3H), 0.91 (d, 3H), 0.86 (d, 3H).

Ejemplo 41

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benciloxi-1H-indol-2-carboxílico

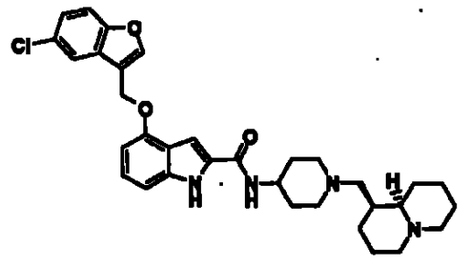


365

Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-benciloxi-1H-indol-2-carboxílico y la amina 5. MS (ESI): 475.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.16 (d, 1H), 7.3-7.54 (m, 5H), 7.26 (d, 1H), 7.06 (t, 1H), 7.0 (d, 1H), 6.6 (d, 1H), 5.18 (s, 2H), 3.74 (m, 1H), 2.86 (m, 2H), 2.47-2.62 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.45-1.64 (m, 10H).

Ejemplo 42

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

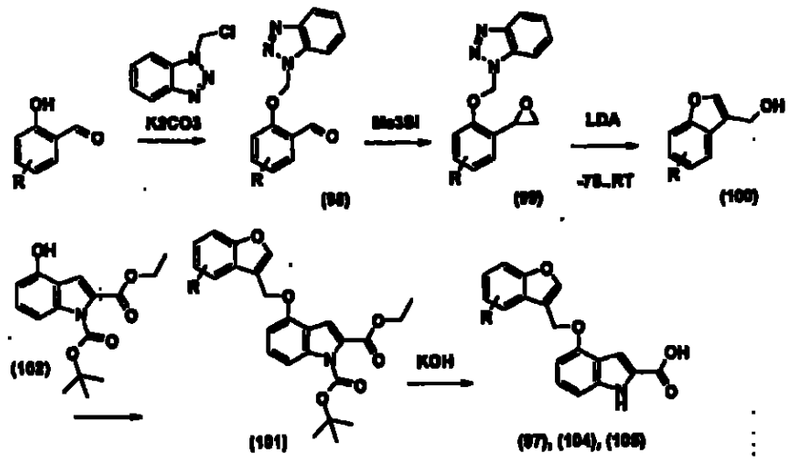


Este compuesto se sintetiza a partir del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-carboxílico (97) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 200 miligramos (59 por ciento). MS (ESI): 575 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 m(s, 1H), 10.1-10.7 (m, 2H), 8.5 (t, 1H), 8.24 (s, 1H), 7.75 (d, 1H), 7.68 (d, 1H), 7.37 (dd, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.8-3.6 (m, 14H), 1.3-2.1 (m, 12H).

366

Esquema de Reacción 13:



Síntesis del 2-etiléster de 1-terbutil-éster del ácido 4-hidroxi-indol-1,2-dicarboxílico (102):

(1) Paso A: 2-etiléster de 1-terbutil-éster del ácido 4-benciloxi-indol-1,2-dicarboxílico (103)

El etiléster del ácido 4-benciloxi-1H-indol-2-carboxílico (50 miligramos, 169.3 milimoles) se disuelve en 500 mililitros de acetato de etilo, y se agrega DMAP (141 miligramos, 3.4 milimoles). Luego la mezcla se enfría a 0°C, y se agrega por goteo BOC_2O (36.9 gramos, 169.3 milimoles), disuelto en 20 mililitros de acetato de etilo. Después de que se termina la adición, la mezcla de reacción se deja agitándose durante la noche a temperatura ambiente. La mezcla se lava con ácido tartárico 1M y salmuera. Las capas orgánicas se secan sobre sulfato de sodio, y se evaporan.

Rendimiento: 72 gramos de un aceite incoloro, el cual se utiliza en el siguiente paso sin mayor purificación.

MS (ESI): 396 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.51 (m, 1H), 7.47 (m, 2H), 7.40 (m, 1H), 7.38 (m, 2H), 7.31 (m, 1H), 7.21 (s, 1H), 6.92 (d, 1H), 5.26 (s, 2H), 4.28 (q, 2H), 1.56 (s, 9H), 1.31 (t, 3H).

(2) Paso B: 2-etiléster de 1-terbutiléster del ácido 4-hidroxi-indol-1,2-dicarboxílico (102)

El 103 (46.2 gramos, 116.8 milimoles) se disuelve en etanol (300 mililitros), y después de la adición de formiato de amonio (8.3 gramos, 128.5 milimoles) y de Pd-C a 10 por ciento (5 gramos), la mezcla se agita a temperatura ambiente durante 1 hora. Luego la mezcla se filtra. La evaporación bajo presión reducida dio 6.89 gramos de un sólido blanco, el cual se purifica adicionalmente mediante recristalización a partir de éter/hexanos.

Rendimiento: 27.75 gramos (78 por ciento). MS (ESI): 304 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 10.1 (s, 1H), 7.38 (d, 1H), 7.25 (s, 1H), 7.23 (dd, 1H), 6.65 (d, 1H), 4.3 (q, 2H), 1.55 (s, 9H), 1.3 (t, 3H).

Síntesis del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (97):

(1) Paso A: 2-(benzotriazol-1-ilmetoxi)-5-cloro-benzaldehído (98).

Se disuelve 5-cloro-2-hidroxi-benzaldehído (8.45 gramos, 54 milimoles) en N,N-dimetilformamida (100 mililitros), y después de la adición de 1-(clorometil)-1H-benzotriazol (9.96 gramos, 59.4 milimoles) y K_2CO_3 (9.7 gramos, 70.2 milimoles), la mezcla se agita a 45°C durante 1 hora (control con cromatografía de capa delgada). Luego la mezcla se evapora bajo un alto vacío. El residuo se diluye

con acetato de etilo, se lava con salmuera, y se seca sobre Na_2SO_4. La evaporación dio 3.9 gramos de un sólido incoloro. El producto se utiliza en el siguiente paso sin mayor purificación.

Rendimiento: 17 gramos (100 por ciento) de un sólido blanco. MS (ESI): 288 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 10.01 (s, 1H), 8.08 (d, 1H), 7.97 (d, 1H), 7.78 (dd, 1H), 7.68 (d, 1H), 7.62 (dd, 1H), 7.55 (d, 1H), 7.43 (dd, 1H), 6.95 (s, 2H).

(2) Paso B: 1-(4-cloro-2-oxiranil-fenoximetil)-1H-benzotriazol (99).

El 98 (15.5 gramos, 54 milimoles) se disuelve en 150 mililitros de DCM y 150 mililitros de una solución acuosa de hidróxido de sodio al 40 por ciento. Después de la adición de yoduro de trimetilsulfonio (14.3 gramos, 70.2 milimoles) y yoduro de tetrabutilamonio (1.4 gramos, 3.8 milimoles), la mezcla se pone a reflujo durante 18 horas. La mezcla de reacción se diluye con DCM, se lava con agua, y las capas orgánicas se secan sobre Na_2SO_4. La evaporación dio 18.7 gramos de un aceite amarillo, el cual se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, acetato de etilo/hexanos, 3:7).

Rendimiento: 11.7 gramos (72 por ciento) de un aceite incoloro. MS (ESI): 302 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.08 (d, 1H), 7.92 (d, 1H), 7.62 (dd, 1H), 7.5 (dd, 1H), 7.45 (dd, 1H), 7.4 (dd, 1H), 6.92 (d, 1H), 6.83 (dd, 1H), 3.8 (m, 1H), 2.8 (dd, 2H), 2.48 (dd, 1H).

(3) Paso C: (5-cloro-benzofuran-3-il)-metanol (100).

El 99 (25.7 gramos, 85.1 milimoles) se disuelve en 300

369

mililitros de tetrahidrofurano y se enfría a -78°C. Se agrega por goteo una solución 2M de LDA en tetrahidrofurano (93.7 mililitros, 187.4 milimoles) dentro de 45 minutos. La mezcla de reacción se deja calentar a temperatura ambiente dentro de 17 horas. Luego la mezcla de reacción se apaga con una solución acuosa saturada de cloruro de amonio, y se evapora bajo presión reducida. El residuo se diluye con acetato de etilo, se lava con agua y salmuera, y se seca sobre sulfato de sodio. La evaporación dio 17.2 gramos de una resina castaña, la cual se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, acetato de etilo/hexanos, 2:8).

Rendimiento: 10.4 miligramos de un sólido blanco (67 por ciento). MS (ESI): 181 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 7.91 (d, 1H), 7.72 (d, 1H), 7.56 (d, 1H), 7.32 (dd, 1H), 5.18 (t, 1H), 4.58 (d, 2H).

(4) Paso D: 2-etiléster de 1-terbutil-éster del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-indol-1,2-dicarboxílico (101).

Se disuelven el 100 (4 gramos, 21.9 milimoles), el 102 (6.7 gramos, 21.9 milimoles), trifenilfosfina (17.3 gramos, 65.8 milimoles), y una solución de azadicarboxilato de dietilo al 40 por ciento (31.8 mililitros, 65.8 milimoles) en tetrahidrofurano, y se enfrían a 0°C. Luego se agrega por goteo una solución de N-etildi-isopropilamina (11.2 mililitros, 65.8 milimoles) en tetrahidrofurano. Después de que se termina la adición, la mezcla se agita a temperatura ambiente durante 2 horas. Luego la mezcla se evapora bajo presión reducida. El residuo se diluye con acetato de etilo, se lava con una solución

370

saturada de $NaHCO_3$, y se seca sobre Na_2SO_4. El producto crudo se purifica mediante cromatografía por evaporación (acetato de etilo/hexanos (3:7), gel de sílice).

Rendimiento: 7.7 gramos (75 por ciento) de un aceite ligeramente coloreado. MS (ESI): 469 $[M]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.27 (s, 1H), 7.79 (d, 1H), 7.63 (d, 1H), 7.53 (d, 1H), 7.40 (d, 1H), 7.36 (dd, 1H), 7.21 (s, 1H), 7.04 (d, 1H), 5.42 (s, 2H), 4.29 (q, 2H), 1.55 (s, 9H), 1.29 (t, 3H).

(5) Paso E: Ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (97).

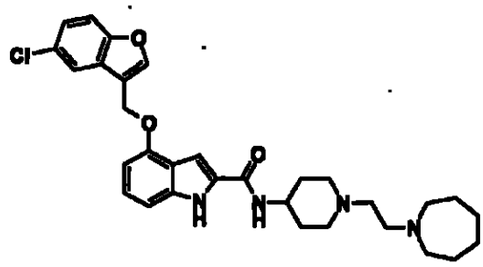
Se disuelve el 101 (7.7 gramos, 16.3 milimoles) en 15 mililitros de una mezcla de 1:1:1 de tetrahidrofurano/agua/etanol, y después de la adición de perlas de KOH (5.4 gramos, 81.9 milimoles), la mezcla se agita durante 2 horas a 85°C. Luego la fase orgánica se evapora bajo presión reducida. El residuo se disuelve en acetato de etilo, se acidifica con HCl 2N, y se filtra. El producto crudo se purifica mediante cristalización a partir de acetato de etilo.

Rendimiento: 4.4 gramos (79 por ciento) de cristales blancos. MS (ESI): 340 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.8 (s, 1H), 11.7 (s, 1H), 8.25 (s, 1H), 7.79 (d, 1H), 7.62 (d, 1H), 7.35 (dd, 1H), 7.15 (dd, 1H), 7.0-7.05 (m, 2H), 6.71 (d, 1H), 5.39 (s, 2H).

Ejemplo 43

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(5-cloro-benz furan-3-ilmet xi)-1H-indol-2-carboxílic

371

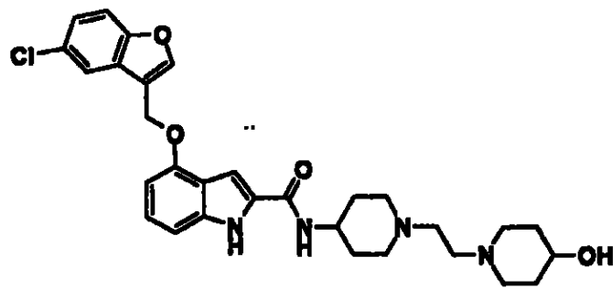


Este compuesto se sintetiza a partir del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 97 (ver el Ejemplo 42), y la amina 5, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 52 miligramos (16 por ciento). MS (ESI): 549 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 10.98 (br s, 1H), 8.12 (s, 1H), 7.68 (d, 1H), 7.53 (d, 1H), 7.0-7.2 (m, 5H), 6.65 (d, 1H), 5.43 (s, 2H), 3.75 (m, 1H), 2.35-2.65 (m, 12H), 2.1 (m, 2H), 1.8 (m, H), 1.5-1.6 (m, 8H).

Ejemplo 44

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 97 (ver el Ejemplo 42), y la amina 21, de una manera análoga al método descrito en el

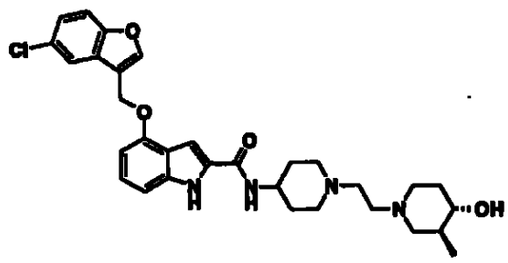
372

Ejemplo 1.

Rendimiento: 50 miligramos (24 por ciento). MS (ESI): 551 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.22 (s, 1H), 8.12 (d, 1H), 7.78 (s, 1H), 7.67 (d, 1H), 7.37 (d, 1H), 7.18 (s, 1H), 7.08 (dd, 1H), 7.02 (d, 1H), 6.67 (m, 1H), 5.33 (s, 2H), 4.49 (b, 1H), 3.7 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.5 (m, 2H), 2.35 (m, 2H), 1.95 (m, 4H), 1.25-1.8 (m, 8H).

Ejemplo 45

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



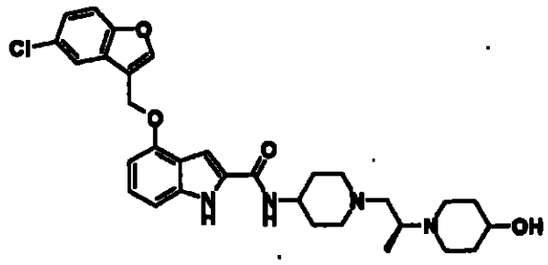
Este compuesto se sintetiza a partir del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 97 (ver el Ejemplo 42), y la amina 14, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 85 miligramos (45 por ciento). MS (ESI): 565 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.29 (br s, 1H), 8.2 (d, 1H), 8.1 (s, 1H), 7.74 (s, 1H), 7.57 (d, 1H), 7.34 (d, 1H), 7.22 (s, 1H), 7.09 (m, 1H), 6.72 (d, 1H), 5.39 (s, 2H), 2.6-4.1 (m, 15H), 1.75-2.2 (m, 8H), 1.00 (d, 3H).

373

Ejemplo 46

Diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



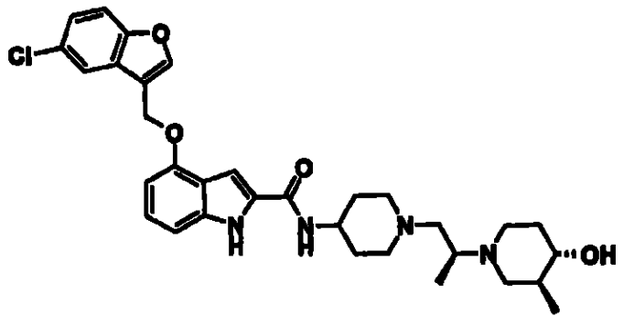
Este compuesto se sintetiza a partir del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 97 (ver el Ejemplo 42), y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 125 miligramos (71 por ciento): MS (ESI): 565 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.3-10.7 (br, 2H), 8.52 (d, 1H), 8.24 (s, 1H), 7.75 (d, 1H), 7.68 (d, 1H), 7.35 (dd, 1H), 7.23 (s, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 2.7-3.7 (m, 12H), 1.7-2.1 (m, 8H), 1.35/1.3 (d, 3H) (rotámeros).

Ejemplo 47

Diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico.

374

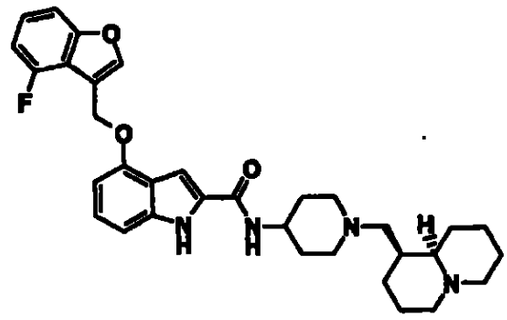


Este compuesto se sintetiza a partir del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 97 (ver el Ejemplo 42), y la amina 56, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 123 miligramos (64 por ciento). MS (ESI): 579 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4-10.6 (br 2H), 8.52 (d, 1H), 8.26 (s, 1H), 7.77 (d, 1H), 7.68 (d, 1H), 7.38 (dd, 1H), 7.23 (s, 1H), 7.12 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 5.1 (br 1H), 4.05 (m, 1H), 2.8-3.9 (m, 13H), 1.9-2.1 (m, 6H), 1.31 (d, 3H), 0.94 (d, 3H).

Ejemplo 48

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



375

Este compuesto se sintetiza a partir del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (104) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 49 miligramos (22.5 por ciento). MS (ESI): 559.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5 (br d, 1H), 10.2 (br d, 1H), 8.45 (m, 1H), 8.25 (s, 1H), 7.5 (d, 1H), 7.38 (m, 1H), 7.25 (m, 1H), 7.1 (m, 2H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.0 (m, 1H), 2.8-3.6 (m, 14H), 1.3-2.1 (m, 12H).

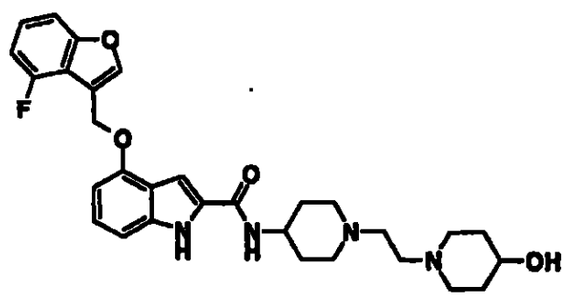
Síntesis del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (104):

Este compuesto se sintetiza a partir de 2-fluoro-6-hidroxi-benzaldehído, de una manera análoga al método descrito para el 97 (ver el Ejemplo 42).

Rendimiento: 220 miligramos (49 por ciento) de cristales blancos. MS (ESI): 324.3 $[M-H]^-$.

Ejemplo 49

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



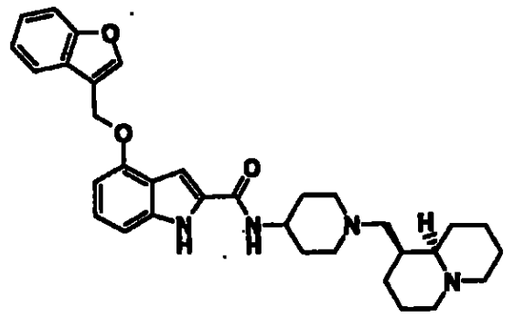
376

Este compuesto se sintetiza a partir del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (104) (ver el Ejemplo 48), y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 100 miligramos (61 por ciento). MS (ESI): 535 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 10.5 (br, 1H), 10.35 (br, 1H), 8.48 (d, 1H), 8.23 (m, 2H), 7.5 (d, 1H), 7.35 (m, 1H), 7.2 (s, 1H), 7.1 (m, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 2.9-3.75 (m, 13H), 1.65-2.1 (m, 8H).

Ejemplo 50

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (105) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 68 miligramos (34 por ciento). MS (ESI): 541 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.56 (s, 1H), 10.5 (br d, 1H), 10.2 (br

d, 1H), 8.5 (t, 1H), 8.18 (s, 1H), 7.72 (d, 1H), 7.6 (d, 1H), 7.25-7.35 (m, 3H), 7.12 (d, 1H), 7.03 (d, 1H), 6.75 (d, 1H), 5.57 (s, 2H), 4.01 (m, 1H), 2.8-3.6 (m, 14H), 1.3-2.1 (m, 12H).

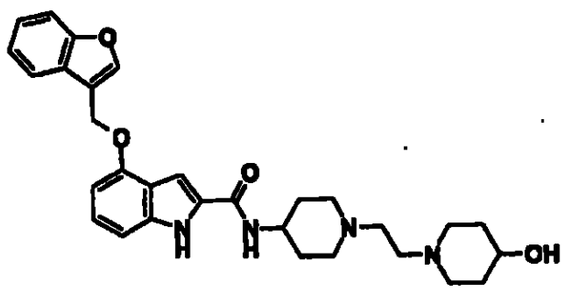
Síntesis del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (105):

Este compuesto se sintetiza a partir de 2-hidroxi-benzaldehído, de una manera análoga al método descrito para el 97 (ver el Ejemplo 42).

MS (ESI): 306 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.7 (s, 1H), 8.15 (s, 1H), 7.73 (d, 1H), 7.58 (d, 1H), 7.33 (dd, 1H), 7.29 (dd, 1H), 7.15 (dd, 1H), 7.05 (s, 1H), 7.02 (d, 1H), 6.73 (d, 1H), 5.38 (s, 2H).

Ejemplo 51

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



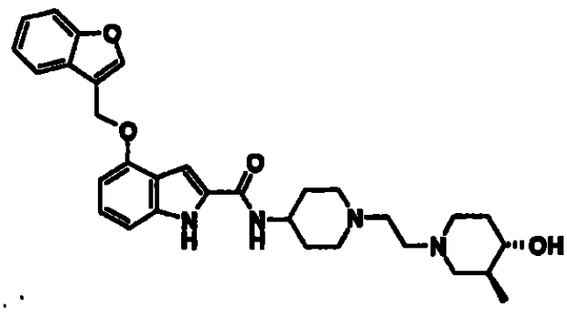
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 105 (ver el Ejemplo 50), y la amina 21.

MS (ESI): 517.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H),

8.17 (s, 1H), 8.1 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.28 (d, 1H), 7.18 (s, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.48 (d, 1H), 3.71 (m, 1H), 3.39 (m, 1H), 2.84 (m, 2H), 2.69 (m, 2H), 2.35 (m, 4H), 1.98 (m, 4H), 1.69 (m, 4H), 148 (m, 2H), 1.34 (m, 2H).

Ejemplo 52

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 105 (ver el Ejemplo 50), y la amina 14.

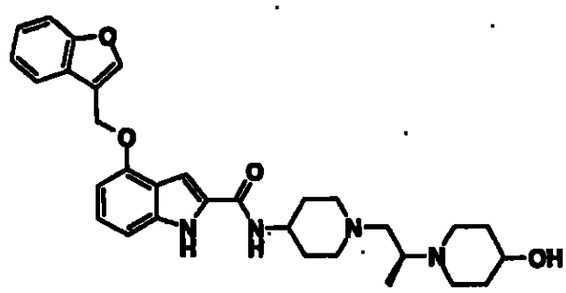
MS (ESI): 531.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.17 (s, 1H), 8.11 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.19 (s, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (d, 2H), 4.47 (d, 1H), 3.7 (m, 1H), 3.3 (m, 1H), 2.65-2.91 (m, 5H), 2.34 (m, 4H), 1.83-2.04 (m, 3H), 165-1.77 (m, 3H), 1.27-1.63 (m, 5H), 0.85 (d, 3H).

Ejemplo 53

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del

379

ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

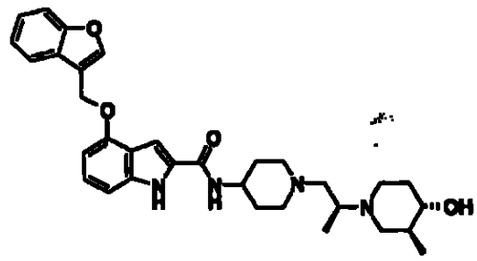


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 105 (ver el Ejemplo 50), y la amina 50.

MS (ESI): 531.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.17 (s, 1H), 8.11 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.19 (d, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.44 (d, 1H), 3.7 (br m, 1H), 3.35 (m, 1H), 2.97 (m, 1H), 2.6-2.9 (m, 4H), 2.0-2.35 (m, 4H), 1.89 (m, 1H), 1.63-1.77 (m, 3H), 1.4-1.6 (m, 3H), 1.2-1.38 (m, 3H), 0.90 (d, 3H).

Ejemplo 54

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo

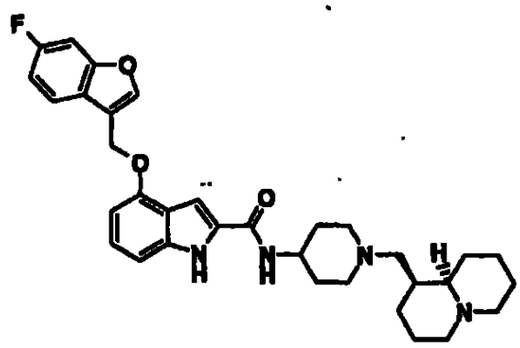
380

1, a partir del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 105 (ver el Ejemplo 50), y la amina 56.

MS (ESI): 545.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.17 (s, 1H), 8.11 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.19 (s, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.43 (d, 1H), 3.71 (m, 1H), 2.59-2.92 (m, 6H), 2.31 (m, 1H), 2.22 (m, 1H), 2.01-2.17 (m, 2H), 1.88 (m, 2H), 1.66-1.76 (m, 3H), 1.2-1.58 (m, 4H), 0.89 (d, 3H), 0.86 (d, 3H).

Ejemplo 55

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



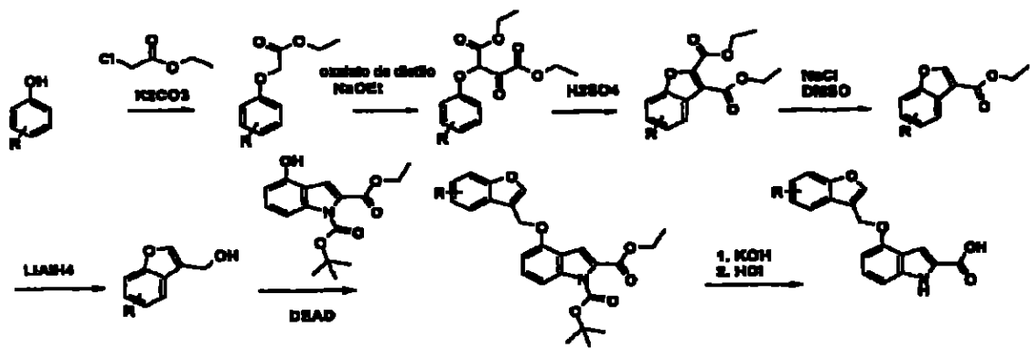
Este compuesto se sintetiza a partir del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (106) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 80 miligramos (41.2 por ciento). MS (ESI): 559 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.63 (br d, 1H), 10.35 (br d, 1H), 8.5 (m, 1H), 8.2 (s, 1H), 7.72 (dd, 1H), 7.58 (dd, 1H), 7.25

381

(m, 1H), 7.2 (m, 1H), 7.1 (d, 1H), 7.03 (d, 1H),6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.6-3.6 (m, 14H), 1.3-2.1 (m, 12H).

Esquema de Reacción 14:



Síntesis de 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (106):

(1) Paso A: Etiléster del ácido (3-fluoro-fenoxi)-acético (107).

Se disuelve 3-fluoro-fenol (100 gramos, 892 milimoles) en acetona (250 mililitros), y después de la adición de etiléster del ácido cloroacético (114 mililitros, 1.07 moles) y K_2CO_3 (249 gramos, 1.78 moles), la mezcla se pone a reflujo durante 24 horas. Después de enfriar a 0°C, la mezcla se filtra, y el filtrado se evapora bajo presión reducida. Rendimiento: 198 gramos (100 por ciento) de un aceite rojo.

(2) Paso B: Dietil-éster del ácido 2-(3-fluoro-fenoxi)-3-oxo-succínico (108)

El NaH al 60 por ciento en aceite minera (19.5 gramos, 488.4 milimoles) se cubre con 600 mililitros de dietil-éter seco. Se agrega por goteo etanol (28.1 mililitros, 444 milimoles) dentro de 25

minutos. Luego se agrega por goteo dietil-éster del ácido oxálico (66 mililitros, 488 milimoles) dentro de 20 minutos. Después de 10 minutos de agitación a temperatura ambiente, la mezcla se calienta a reflujo. Se agrega por goteo una solución del 107 (88 gramos, 444 milimoles) en 80 mililitros de dietil-éter seco dentro de 30 minutos, y la mezcla se deja a reflujo durante 1 hora. Después de enfriar a temperatura ambiente, la mezcla de reacción se vierte sobre HCl 2M (400 mililitros)/hielo (400 gramos), y se extrae con dietil-éter. Las capas orgánicas se secan sobre sulfato de sodio, se filtran, y se evaporan. El producto crudo se purifica mediante filtración sobre gel de sílice (acetato de etilo/hexano, 1:1). La evaporación dio 140 gramos de un aceite rojo. El aceite mineral se pudo remover utilizando un embudo de separación. Rendimiento: 132 gramos (100 por ciento).

(3) Paso C: Dietil-éster del ácido 6-fluoro-benzofuran-2,3-dicarboxílico (109)

Se disuelve el 108 (66 gramos, 221.3 milimoles) en 245 mililitros de ácido sulfúrico concentrado y enfriado (-15°C), y se agita durante 3 horas, mientras que se calienta lentamente la mezcla de reacción a temperatura ambiente. Luego la mezcla se vierte sobre 1 kilogramo de hielo, y se extrae con dietil-éter. Las capas orgánicas se lavan con salmuera, se secan sobre sulfato de sodio, se filtran y se evaporan. El producto crudo se utiliza en el siguiente paso sin mayor purificación.

Rendimiento: 19.7 gramos (32 por ciento) de un aceite amarillo. MS

383

(ESI): 281 $[M+H]^+$. 1H-RMN (DMSO-d_6): δ (ppm) 7.88 (dd, 1H), 7.82 (dd, 1H), 7.35 (ddd, 1H), 4.38 (m, 4H), 1.33 (t, 3H), 1.32 (t, 6H). La ciclación dio exclusivamente el benzofurano 6-sustituido.

(4) Paso D: Etil-éster del ácido 6-fluoro-benzofuran-3-carboxílico (110)

Se disuelve el 109 (40 gramos, 142.7 milimoles) en 300 mililitros de sulfóxido de dimetilo, y después de la adición de cloruro de sodio (16.7 gramos, 285.4 milimoles) y agua (5.1 mililitros), la mezcla se agita durante 4 horas a 160°C (temperatura de la mezcla de reacción). Luego la mezcla se deja enfriar y se evapora en un alto vacío. El residuo se disuelve en acetato de etilo, se lava con agua y salmuera, y se seca sobre sulfato de sodio. La evaporación dio 14.8 gramos de un aceite rojo, el cual se purifica adicionalmente mediante filtración sobre gel de sílice (acetato de etilo/hexanos, 2:8). Rendimiento: 7.8 gramos (26 por ciento) de un sólido amarillo. MS (ESI): 208 $[M]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.77 (s, 1H), 7.92 (dd, 1H), 7.68 (dd, 1H), 7.29 (ddd, 1H), 4.35 (q, 2H), 1.32 (t, 3H).

(5) Paso E: (6-fluoro-benzofuran-3-il)-metanol (111)

Se diluye una solución de LiAlH4 en tetrahidrofurano (75.9 mililitros, 75.9 milimoles) con 100 mililitros de tetrahidrofurano, y se enfría a 0°C. Se disuelve el 110 (7.9 gramos, 37.9 milimoles) en 100 mililitros de tetrahidrofurano, y se agrega por goteo dentro de 30 minutos. Después de que se termina la adición, la mezcla se deja agitándose a temperatura ambiente durante 2 horas. Luego la mezcla de reacción se enfría a -15°C, y se agregan muy lentamente 10

384

mililitros de una solución de NaOH 1M. La mezcla se filtra sobre Celite, y la evaporación bajo presión reducida dio 5.3 gramos de un aceite amarillo.

(6) Paso F: 2-etil-éster de 1-terbutil-éster del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-indol-1,2-dicarboxílico (112)

Se disuelven el 111 (2 gramos, 12 milimoles), el 102 (3.7 gramos, 12 milimoles), trifenilfosfina (9.4 gramos, 36.1 milimoles) de DIPEA (62 mililitros, 36.1 milimoles) en 50 mililitros de tetrahidrofurano, y se enfrían a 0°C. Luego se agrega por goteo una solución de azodicarboxilato de etilo al 40 por ciento en tetrahidrofurano (15.7 mililitros, 36.1 milimoles). Después de que se termina la adición, la mezcla se agita durante 16 horas (control con cromatografía de capa delgada) a temperatura ambiente. Entonces la mezcla se evapora bajo presión reducida. El residuo se diluye con acetato de etilo, se lava con una solución saturada de $NaHCO_3$ y NaCl, y se seca sobre Na_2SO_4. El producto crudo se purifica mediante cromatografía por evaporación (acetato de etilo/hexanos, 1:9), gel de sílice).

Rendimiento: 1.2 gramos (22 por ciento) de un aceite rojo. MS (ESI): 454 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.22 (s, 1H), 7.73 (dd, 1H), 7.58 (dd, 1H), 7.53 (d, 1H), 7.38-7.40 (m, 2H), 7.15-77.25 (m, 1H), 7.05 (d, 1H), 5.43 (s, 2H), 4.05 (q, 2H), 155 (s, 9H), 1.29 (t, 3H).

(7) Paso G: Ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

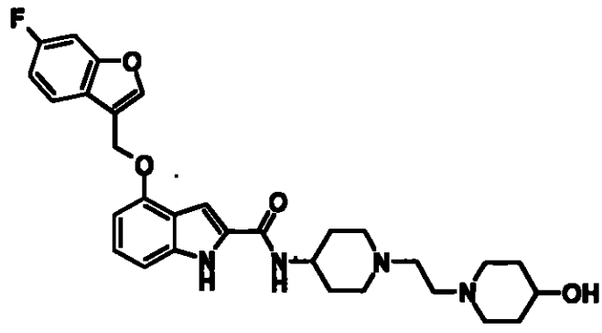
Se disuelve el 112 (1.2 gramos, 2.6 milimoles) en 30 mililitros

385

de una mezcla de 1:1:1 de tetrahidrofurano, etanol, y agua. Después de la adición de perlas de KOH (742 miligramos, 13.2 milimoles), la mezcla se agita durante 2 horas (control con cromatografía de capa delgada) a 85°C. Luego se remueve el solvente orgánico bajo presión reducida. El residuo se enfría a 0°C, y se trata con HCl 2M. El producto crudo se filtra y se seca bajo un alto vacío. El producto crudo (800 miligramos) se recristaliza a partir de acetato de etilo. Rendimiento: 520 miligramos (60 por ciento) de cristales incoloros. MS (ESI): 324 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.7 (s, 1H), 8.18 (s, 1H), 7.73 (dd, 1H), 7.57 (dd, 1H), 7.18 (dd, 1H), 7.15 (d, 1H), 7.05 (s, 1H), 7.02 (d, 1H), 6.72 (d, 1H), 5.38 (s, 2H).

Ejemplo 56

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



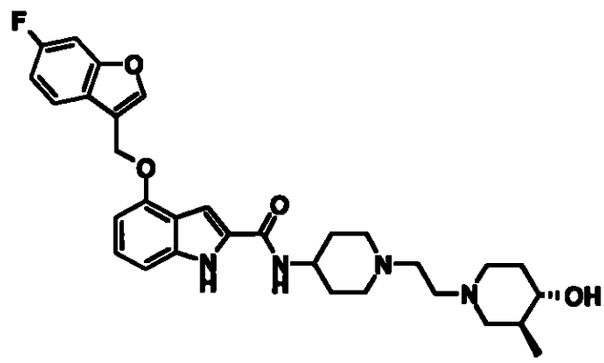
Este compuesto se sintetiza a partir del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 106 (ver el Ejemplo 55) y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

386

Rendimiento: 70 miligramos (38 por ciento). MS (ESI): 535 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.55 (br, 1H), 10.45 (br, 1H), 8.5 (br d, 1H), 8.2 (s, 1H), 7.7 (dd, 1H), 7.6 (dd, 2H), 7.15-7.25 (m, 2H), 7.1 (dd, 1H), 7.03 (d, 1H), 5.35 (s, 2H), 5.0 (br 1H), 4.05 (m, 1H), 2.9-3.7 (m, 13H), 1.7-2.1 (m, 8H).

Ejemplo 57

Diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico.



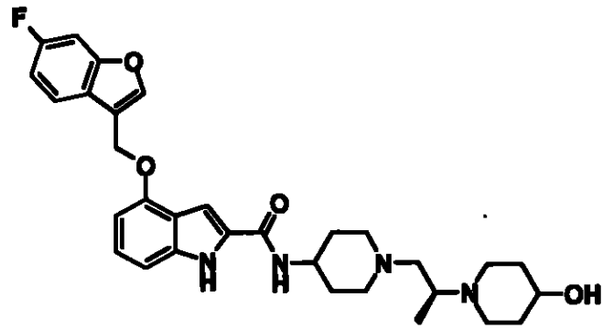
Este compuesto se sintetiza a partir del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 106 (ver el Ejemplo 55) y la amina 14, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 135 miligramos (71 por ciento). MS (ESI): 549 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.65 (br, 2H), 8.52 (d, 1H), 8.2 (s, 1H), 7.72 (dd, 1H), 7.58 (dd, 1H), 7.24 (s, 1H), 7.2 (m, 1H), 7.1 (dd, 1H), 7.04 (d, 1H), 6.72 d, 1H), 5.35 (s, 2H), 2.6-

4.2 (m, 14H), 1.75-2.2 (m, 8H), 0.93 (d, 3H).

Ejemplo 58

Diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

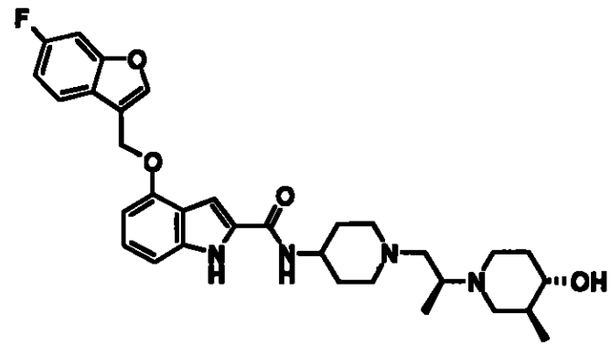


Este compuesto se sintetiza a partir del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 106 (ver el Ejemplo 55) y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 75 miligramos (39 por ciento). MS (ESI): 549 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.3-10.7 (br, 2H), 8.53 (d, 1H), 8.2 (s, 1H), 7.72 (dd, 1H), 7.58 (dd, 1H), 7.24 (s, 1H), 7.2 (m, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 5.1 (br, 1H), 2.8-41 (m, 13H), 1.7-2.2 (m, 8H), 1.35/13 (d, 3H) (rotámeros).

Ejemplo 59

{1-[(S)-2-((3S,4S)-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

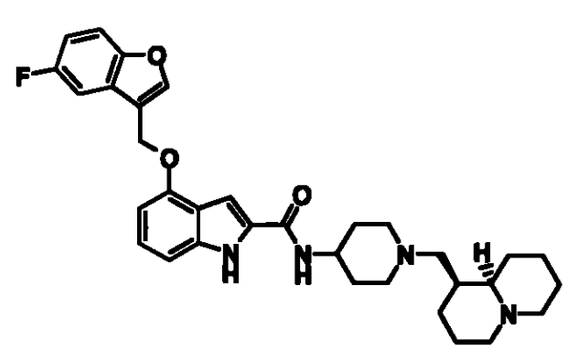


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 106 (ver el Ejemplo 55) y la amina 56.

MS (ESI): 463.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.19 (s, 1H), 8.11 (d, 1H), 7.71 (dd, 1H), 7.58 (dd, 1H), 719 (m, 2H), 7.09 (t, 1H), 7.01 (d, 1H), 6.7 (d, 1H), 5.34 (s, 2H), 4.43 (d, 1H), 3.71 (m, 1H), 2.58-2.92 (m, 6H), 2.31 (m, 1H), 2.22 (m, 1H), 2.02-2.18 (m, 2H), 1.89 (m, 2H), 1.64-1.78 (m, 3H), 1.42-1.59 (m, 2H), 1.2-1.4 (m, 2H), .9 (d, 3H), 0.86 (d, 3H).

Ejemplo 60

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



389

Este compuesto se sintetiza a partir del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 113 (para la preparación, ver más adelante) y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

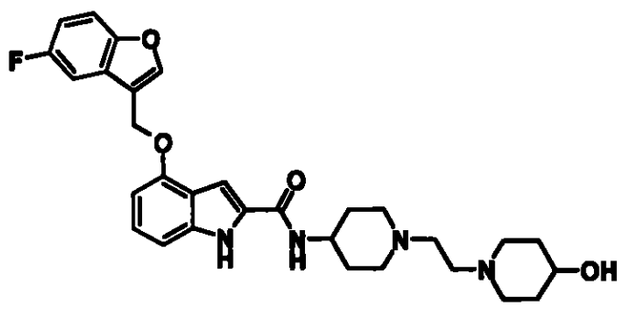
Rendimiento: 840 miligramos (72.5 por ciento). MS (ESI): 559 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.23 (s, 1H), 8.1 (d, 1H), 7.64 (dd, 1H), 7.48 (dd, 1H), 7.17 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.68 (d, 1H), 5.35 (s, 2H), 3.75 (m, 1H), 2.65-2.85 (m, 4H), 2.47 (m, 1H), 2.25 (dd, 1H), 1.2-2.05 (m, 20H).

Síntesis del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (113):

Este compuesto se sintetiza a partir del 4-fluoro-fenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55). MS (ESI): 324.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.81 (br s, 1H), 11.7 (s, 1H), 8.24 (s, 1H), 7.64 (dd, 1H), 7.51 (dd, 1H), 7.15 (m, 2H), 7.05 (m, 2H), 6.7 (d, 1H), 5.37 (s, 2H).

Ejemplo 61

Diclorhidrato de [1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



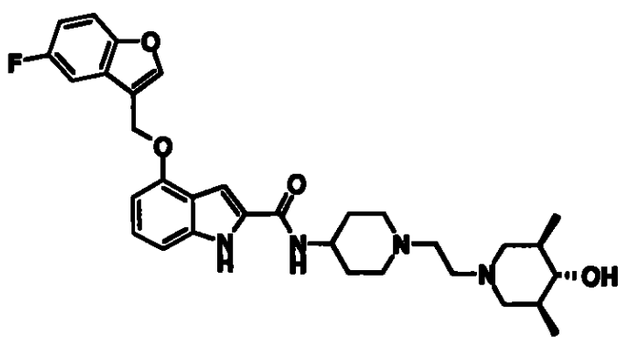
390

Este compuesto se sintetiza a partir del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 113 (ver el Ejemplo 60) y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 160 miligramos (57 por ciento). MS (ESI): 535 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.65 (br, 1H), 10.55 (br, 1H), 8.51 (br d, 1H), 8.25 (s, 1H), 7.65 (m, 1H), 7.45 (dd, 2H), 72 (s, 1H), 7.05 - 7.15 (m, 3H), 6.7 (d, 1H), 5.35 (s, 2H), 4.12 (m, 1H), 3.84 (m, 1H), 2.9-3.7 (m, 13H), 1.75 - 2.2 (m, 8H).

Ejemplo 62

Diclorhidrato de {1-[2-((3R,4R,5S)-4-hidroxi-3,5-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 113 (ver el Ejemplo 60) y la amina 41, de una manera análoga al método descrito en el Ejemplo 1.

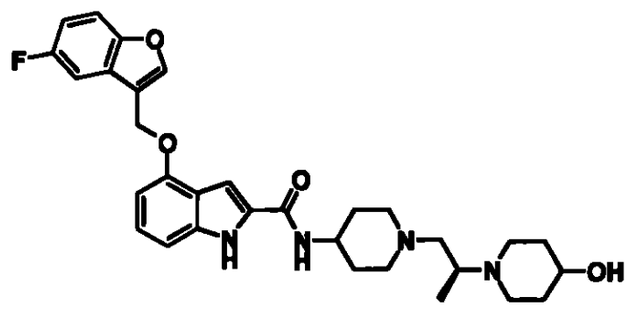
Rendimiento: 110 miligramos (56 por ciento). MS (ESI): 563 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5-10.7 (br 2H),

391

8.5 (d, 1H), 8.22 (s, 1H), 7.61 (dd, 1H), 7.49 (dd, 1H), 7.2 (m, 2H), 7.1 (d, 1H), 7.02 (d, 1H), 67 (d, 1H), 5.32 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 2.6-3.8 (m, 13H), 1.8-2.1 (m, 6H), 0.93 (d, 6H).

Ejemplo 63

Diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 113 (ver el Ejemplo 60) y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

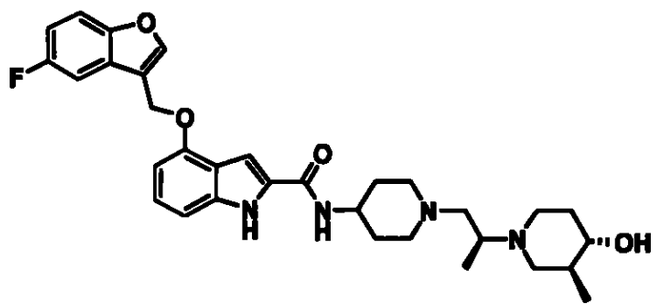
Rendimiento: 85 miligramos (45 por ciento). MS (ESI): 549 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.2 - 10.6 (br, 2H), 8.5 (d, 1H), 8.24 (s, 1H), 7.65 (dd, 1H), 75 (m, 1H), 7.15-73 (m, 2H), 7.1 (dd, 1H), 7.03 (dd, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 5.04 (br, 1H), 2.8-4.1 (m, 13H), 1.7-2.2 (m, 8H), 1.35/13 (d, 3H) (rotámeros).

Ejemplo 64

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-

392

1H-ind l-2-carboxílico

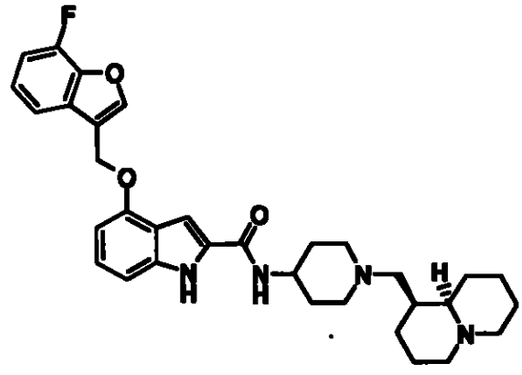


Este compuesto se sintetiza una manera análoga al Ejemplo 1, a partir del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 113 (ver el Ejemplo 60) y la amina 56.

MS (ESI): 563.1 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 7.95 (s, 1H), 7.48 (dd, 1H), 7.43 (dd, 1H), 7.21 (s, 1H), 7.15 (t, 1H), 7.02-7.12 (m, 2H), 6.69 (d, 1H), 5.34 (s, 2H), 3.86 (m, 1H), 2.72-3.12 (m, 6H), 2.51 (m, 1H), 2.17-2.41 (m, 3H), 1.97-2.15 (m, 2H), 1.81-1.96 (m, 3H), 1.45-1.76 (m, 4H), 1.05 (d, 3H), 0.98 (d, 3H).

Ejemplo 65

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(7-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



393

Este compuesto se sintetiza a partir del ácido 4-(7-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (114) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 194 miligramos (40 por ciento). MS (ESI): 559 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.2-10.7 (br, 2H), 8.45 (dd, 1H), 8.28 (s, 1H), 7.58 (dd, 1H), 7.2-7.3 (m, 3H), 7.1 (m, 1H), 7.05 (d, 1H), 6.72 (d, 1H), 5.38 (s, 2H), 4.0 (m, 1H), 2.65-2.85 (m, 6H), 1.2-2.05 (m, 20H).

Síntesis del ácido 4-(7-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (114):

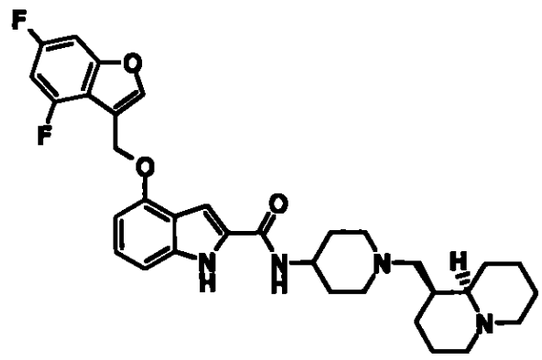
Este compuesto se sintetiza a partir del 2-fluoro-fenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55).

MS (ESI): 324.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.85 (br s, 1H), 11.75 (s, 1H), 8.25 (s, 1H), 7.58 (dd, 1H), 7.2-7.3 (m, 2H), 7.15 (dd, 1H), 7.05 (s, 1H), 7.02 (d, 1H), 6.72 (d, 1H), 5.4 (s, 2H).

Ejemplo 66

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico.

394



Este compuesto se sintetiza a partir del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (115) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 155 miligramos (82 por ciento). MS (ESI): 577 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5 (br d, 1H), 10.2 (br d, 1H), 8.45 (br d, 1H), 8.25 (s, 1H), 7.55 (d, 1H), 7.2-7.25 (m, 2H), 7.1 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.0 (m, 1H), 2.8-3.6 (m, 14H), 1.3-2.1 (m, 12H).

Síntesis del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (115):

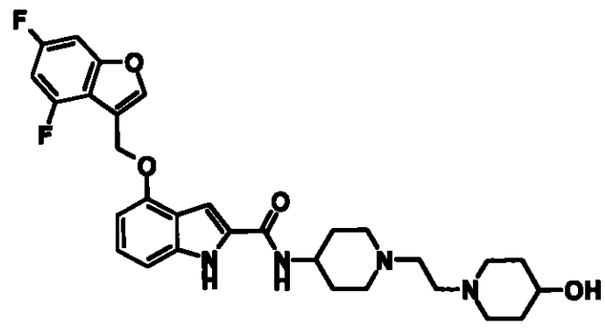
Este compuesto se sintetiza a partir del 3,5-difluoro-fenol de una manera análoga a método descrito para el 106 (ver el Ejemplo 55).

MS (ESI): 342 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.6 (s, 1H), 8.24 (s, 1H), 7.51 (dd, 1H), 7.2 (dd, 1H), 7.15 (dd, 1H), 7.04 (d, 1H), 7.02 (s, 1H), 6.7 (d, 1H), 5.32 (s, 2H).

395

Ejemplo 67

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



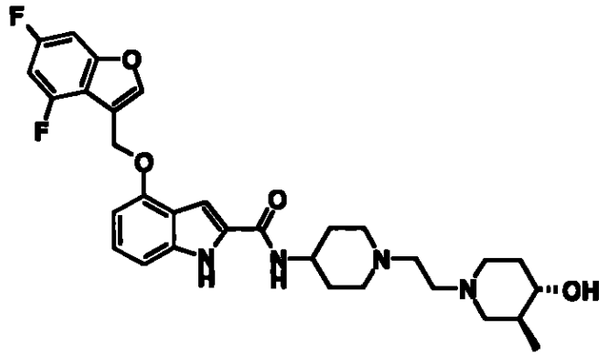
Este compuesto se sintetiza a partir del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 115 (ver el Ejemplo 66), y la amina 21, de una manera análoga a la descrita en el Ejemplo 1.

Rendimiento: 90 miligramos (49 por ciento). MS (ESI): 553 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.5 (br, 1H), 10.35 (br, 1H), 8.48 (br d, 1H), 8.25 (s, 1H), 7.54 (d, 1H), 7.2 (m, 2H), 7.12 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 4.07 (m, 1H), 2.9-3.75 (m, 13H), 1.65-2.1 (m, 8H).

Ejemplo 68

Diclorhidrato de {1-`2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-1-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

396

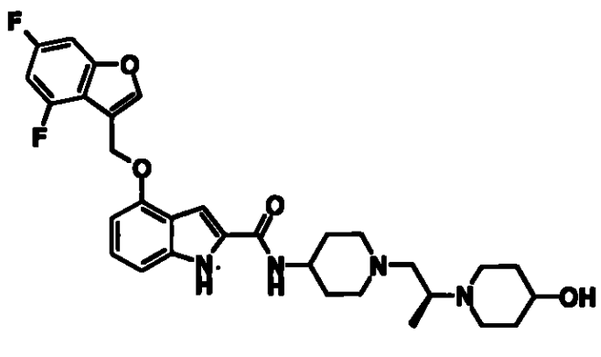


Este compuesto se sintetiza a partir del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (115) (ver el Ejemplo 66), y la amina 14, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 125 miligramos (67 por ciento). MS (ESI): 567 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.65 (br, 2H), 8.5 (d, 1H), 8.25 (s, 1H), 7.53 (dd, 1H), 7.2-7.3 (m, 2H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 2.6-4.1 (m, 14H), 1.75-2.2 (m, 8H), 0.93 (d, 3H).

Ejemplo 69

Diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

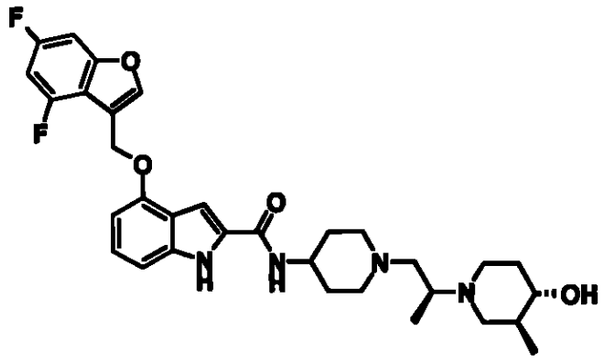


Este compuesto se sintetiza a partir del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 115 (ver el Ejemplo 66), y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 105 miligramos (56 por ciento). MS (ESI): 567 $[M+H]^+$, 1H-RMN (120°C, DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.3-10.7 (br, 2H), 8.52 (d, 1H), 8.26 (s, 1H), 7.53 (d, 1H), 7.2 (m, 2H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 2.9-3.9 (m, 12H), 1.7-2.2 (m, 8H), 1.34 (d, 3H).

Ejemplo 70

Diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 115 (ver el Ejemplo 66), y la amina 56, de una manera análoga al método descrito en el Ejemplo 1.

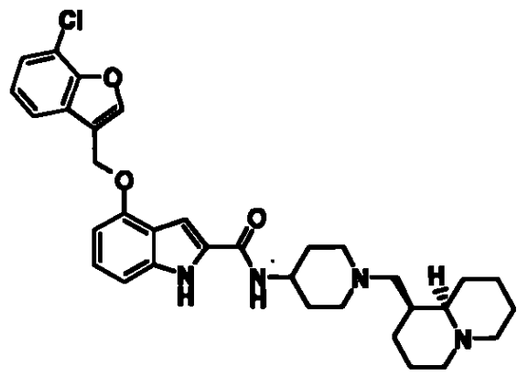
Rendimiento: 130 miligramos (68 por ciento). MS (ESI): 581 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4-10.6 (br, 2H), 8.5 (d,

398
394

1H), 8.27 (, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 2.8-3.9 (m, 13H), 1.9-2.1 (m, 6H), 1.3 (d, 3H), 0.93 (d, 3H).

Ejemplo 71

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(7-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(7-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (116) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 55 miligramos (29 por ciento). MS (ESI): 575 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.1-10.6 (br, 2H), 8.5 (dd, 1H), 8.3 (s, 1H), 7.7 (d, 1H), 7.48 (d, 1H), 7.32 (dd, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.05 (d, 1H), 6.7 (d, 1H), 5.38 (s, 2H), 2.65 (s, 2H), 4.0 (m, 1H), 2.65-2.85 (m, 6H), 1.2-2.05 (m, 20H).

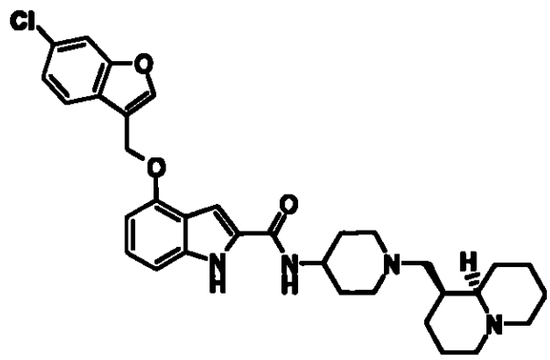
Síntesis del ácido 4-(7-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílic (116):

399

Este compuesto se sintetiza a partir de 2-cloro-fenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55). MS (ESI): 340 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 10.86 (s, 1H), 8.25 (s, 1H), 7.71 (d, 1H), 7.42 (d, 1H), 7.30 (dd, 1H), 6.93 (m, 2H), 6.58 (d, 1H), 6.34 (s, 1H), 5.36 (s, 2H) (sal de potasio).

Ejemplo 72

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (117) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 85 miligramos (49.8 por ciento). MS (ESI): 575 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br d, 1H), 10.3 (br d, 1H), 8.49 (br dd, 1H), 8.22 (s, 1H), 7.8 (d, 1H), 7.72 (d, 1H), 7.38 (dd, 1H), 7.25 (m, 1H), 7.1 (m, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.8-38 (m, 14H), 1.3-2.1 (m, 12H).

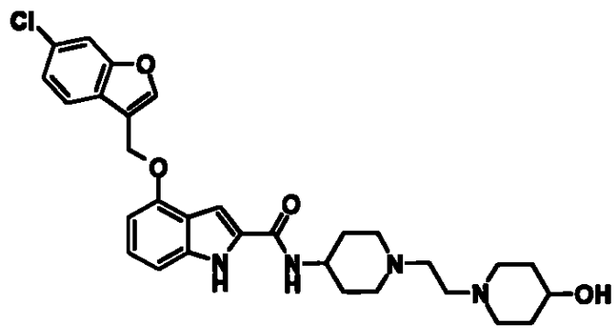
400

Síntesis del ácid 4-(6-clor -benz furan-3-ilmetoxi)-1H-indol-2-carboxílico (117):

Este compuesto se sintetiza a partir de 3-cloro-fenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55). La ciclación con ácido sulfúrico concentrado (Paso C), dio una mezcla de 1:1 de los benzofuranos 4- y 6-sustituidos, los cuales se pudieron separar en el paso D. MS (ESI): 340 [M-H].

Ejemplo 73

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



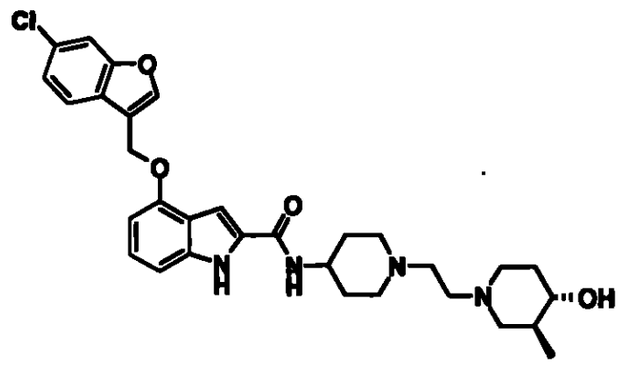
Este compuesto se sintetiza a partir del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 117 (ver el Ejemplo 72), y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 63 miligramos (34 por ciento). MS (ESI): 551 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.22 (s, 1H), 8.15 (br d, 1H), 7.81 (s, 1H), 7.75 (d, 1H), 7.35 (dd, 1H), 7.18 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.75 (b, 1H), 2.1-3.9 (m, 14H), 1.4-1.8 (m, 8H).

401

Ejemplo 74

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida de 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



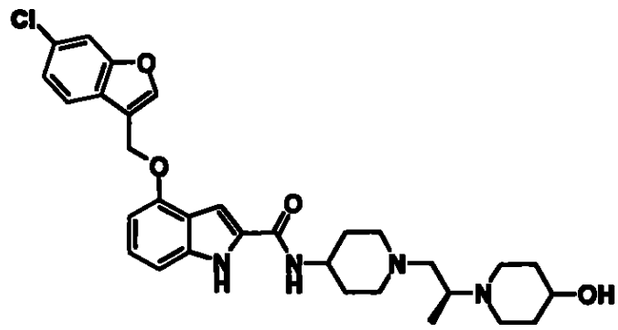
Este compuesto se sintetiza a partir del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 117 (ver el Ejemplo 72), y la amina 14, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 55 miligramos (32 por ciento). MS (ESI): 565 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.5 (br, 2H), 8.48 (d, 1H), 8.22 (s, 1H), 7.80 (s, 1H), 7.70 (d, 1H), 7.37 (d, 1H), 7.22 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.71 (d, 1H), 5.34 (s, 2H), 2.6-42 (m, 14H), 1.75-2.2 (m, 8H), 0.93 (d, 3H).

Ejemplo 75

Diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

402

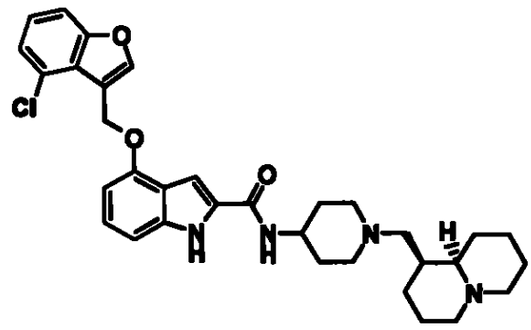


Este compuesto se sintetiza a partir del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 117 (ver el Ejemplo 72), y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 85 miligramos (46 por ciento). MS (ESI): 565 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.2-10.6 (br, 2H), 8.5 (d, 1H), 8.21 (s, 1H), 7.8 (d, 1H), 7.7 (s, 1H), 7.35 (dd, 1H), 7.24 (s, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 5.0 (br, 1H), 2.85-4.2 (m, 13H), 1.7-22 (m, 8H), 1.35/1.3 (d, 3H) (rotámeros).

Ejemplo 76

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



403

Este compuesto se sintetiza a partir del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (118) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 230 miligramos (58.8 por ciento). MS (ESI): 575 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br d, 1H), 10.3 (br d, 1H), 8.45 (br dd, 1H), 8.3 (s, 1H), 7.65 (dd, 1H), 7.3-7.4 (m, 2H), 7.25 (m, 1H), 7.1 (m, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.35 (s, 2H), 4.0 (m, 1H), 2.8-3.8 (m, 14H), 1.3-2.1 (m, 12H).

Síntesis del ácido 4-(4-cloro-benzofuran3-ilmetoxi)-1H-indol-2-carboxílico (118):

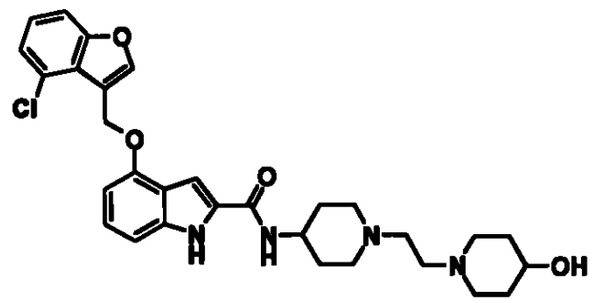
Este compuesto se sintetiza a partir del 3-cloro-fenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55). La ciclación con ácido sulfúrico concentrado (Paso C) dio una mezcla de 1:1 de los benzofuranos 4- y 6-sustituidos, los cuales se pudieron separar en el Paso D.

MS (ESI): 340 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.75 (br s, 1H), 11.7 (s, 1H), 8.31 (s, 1H), 7.6 (dd, 1H), 7.35 (m, 2H), 7.15 (dd, 1H), 7.02 (m, 2H), 6.75 (d, 1H), 5.42 (s, 2H).

Ejemplo 77

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carb xílico

404

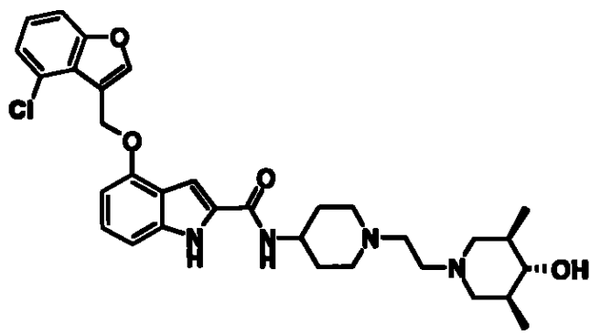


Este compuesto se sintetiza a partir del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 118 (ver el Ejemplo 76), y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 160 miligramos (99 por ciento). MS (ESI): 551 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.52 (s, 1H), 10.35 (br, 1H), 10.2 (br, 1H), 8.5 (br, 1H), 8.31 (s, 1H), 7.63 (d, 1H), 7.36 (m, 2H), 7.22 (s, 1H), 7.11 (dd, 1H), 7.03 (d, 1H), 6.71 (d, 1H), 5.37 (s, 2H), 5.02 (br, 1H), 4.05 (m, 1H), 2.9-3.75 (m, 13H), 1.65-2.1 (m, 8H).

Ejemplo 78

Diclorhidrato de {1-[2-((3R,4R,5S)-4-hidroxi-3,5-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



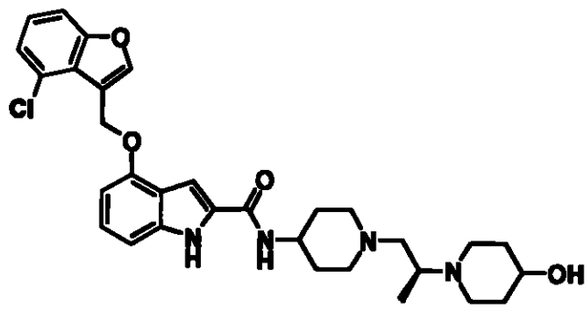
405

Este compuesto se sintetiza a partir del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 118 (ver el Ejemplo 76), y la amina 41, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 45 miligramos (39 por ciento). MS (ESI): 577 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.45-10.7 (br, 2H), 8.47 (d, 1H), 8.32 (s, 1H), 7.65 (d, 1H), 7.35 (m, 2H), 7.21 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 5.0 (br, 1H), 4.05 (m, 1H), 2.6-3.8 (m, 13H), 1.8-2.1 (m, 6H), 0.93 (d, 6H).

Ejemplo 79

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 118 (ver el Ejemplo 76), y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

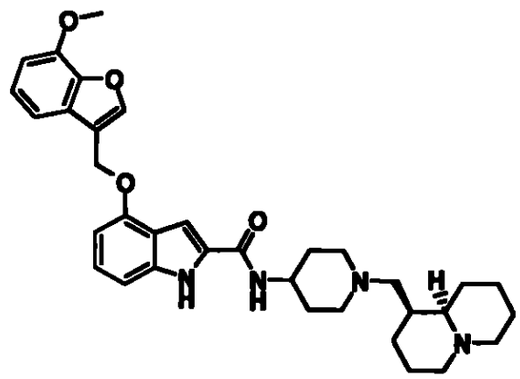
Rendimiento: 20 miligramos (13 por ciento). MS (ESI): 565 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.3 (s, 1H), 8.1 (d, 1H), 7.62 (d, 1H), 7.35 (m, 2H), 7.2 (s, 1H), 7.1 (dd, 1H), 7.0 (d, 1H), 6.7

406

(d, 1H), 5.4 (s, 2H), 45 (br, 1H), 4.05 (m, 1H), 3.7 (m, 1H), 2.6-2.9 (m, 4H), 1.1-2.4 (m, 15H), 0.9 (d, 3H).

Ejemplo 80

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 119 (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 130 miligramos (68.1 por ciento). MS (ESI): 571 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.5 (br d, 1H), 10.2 (r d, 1H), 8.47 (dd, 1H), 8.13 (s, 1H), 7.25 (m, 2H), 7.2 (dd, 1H), 7.09 (d, 1H), 7.02 (d, 1H), 6.95 (d, 1H), 6.72 (d, 1H), 5.32 (s, 2H), 4.0 (m, 1H), 3.83 (s, 3H), 2.8-3.8 (m, 14H), 1.3-2.1 (m, 12H).

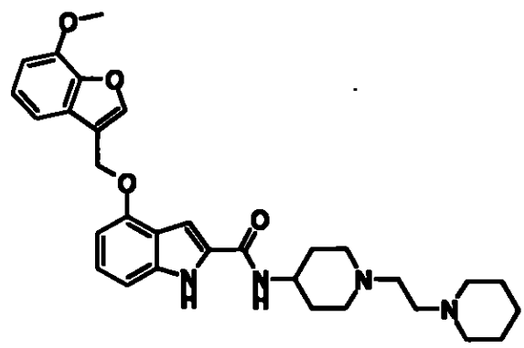
Síntesis del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (119):

Este compuesto se sintetiza a partir del 2-metoxi-fenol, de una

manera análoga al método descrito para el 106 (ver el Ejemplo 55). MS (ESI): 336 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.8 (br s, 1H), 11.54 (br s, 1H), 8.11 (s, 1H), 7.28 (d, 1H), 7.18 (dd, 1H), 7.09 (m, 1H), 7.0 (d, 1H), 6.95 (d, 1H), 6.92 (m, 1H), 6.70 (d, 1H), 5.35 (s, 2H), 3.92 (s, 3H).

Ejemplo 81

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



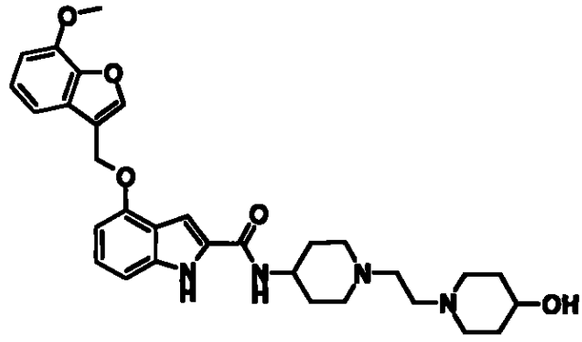
Este compuesto se sintetiza a partir del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 119 (ver el Ejemplo 80), y la amina 1, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 162 miligramos (48 por ciento). MS (ESI): 531 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.53 (s, 1H), 10.55 (br, 1H), 10.31 (br, 1H), 8.49 (d, 1H), 8.12 (s, 1H), 7.25 (dd, 1H), 7.22 (br s, 1H), 7.19 (dd, 1H), 71 (dd, 1H), 7.02 (d, 1H), 7.95 (d, 1H), 6.7 (d, 1H), 5.31 (s, 2H), 4.05 (m, 1H), 3.93 (s, 3H), 3.5-3.8 (m, 8H), 3.1 (m, 2H), 1.7-2.1 (m, 8H), 1.4 (m, 2H).

408

Ejemplo 82

Diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



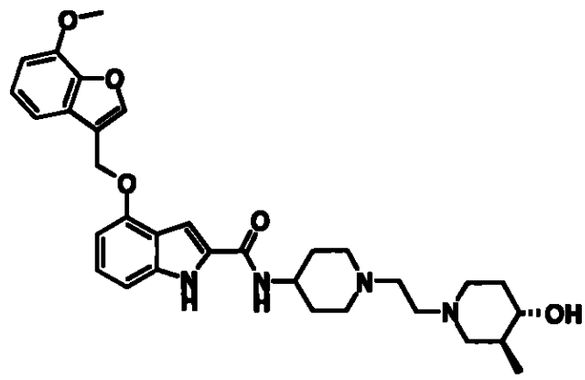
Este compuesto se sintetiza a partir del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 119 (ver el Ejemplo 80), y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 135 miligramos (73 por ciento). MS (ESI): 547 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 10.5 (br, 1H), 10.4 (br, 1H), 8.5 (br, 1H), 8.14 (s, 1H), 7.2-7.3 (m, 3H), 7.1 (dd, 1H), 7.0 (d, 1H), 6.95 (d, 1H), 6.7 (d, 1H) 5.32 (s, 2H), 5.05 (br, 1H), 4.05 (m, 1H), 3.93 (s, 3H), 2.7-37 (m, 13H), 1.6-2.1 (m, 8H).

Ejemplo 83

Diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

409

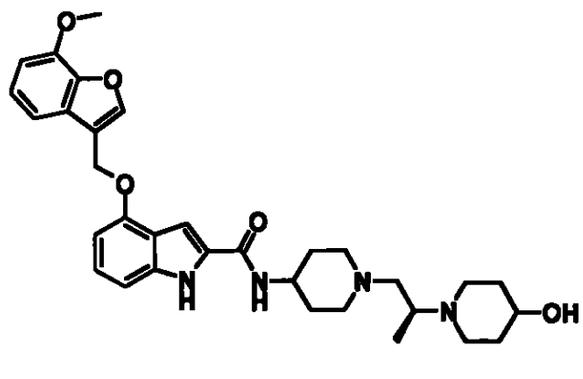


Este compuesto se sintetiza a partir del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 119 (ver el Ejemplo 80), y la amina 14, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 100 miligramos (53 por ciento). MS (ESI): 561 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 8.13 (s, 1H), 7.18 7.3 (m, 3H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.96 (d, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 3.95 (s, 3H), 2.6-4.2 (m, 14H), 1.75-2.2 (m, 8H), 0.93 (d, 3H).

Ejemplo 84

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



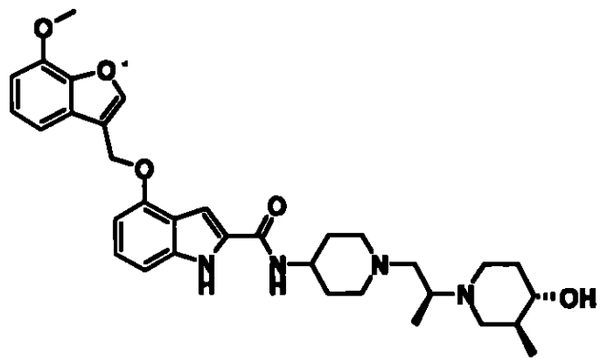
410

Este compuesto se sintetiza a partir del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 119 (ver el Ejemplo 80), y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 166 miligramos (94 por ciento). MS (ESI): 561 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.2-10.6 (br, 2H), 8.5 (d, 1H), 8.14 (s, 1H), 7.28 (d, 1H), 7.23 (s, 1H), 7.22 (dd, 1H), 7.1 (dd, 1H), 7.03 (d, 1H), 6.95 (d, 1H), 6.7 (d, 1H), 5.33 (s, 2H), 5.05 (br, 1H), 3.93 (s, 3H), 2.9-4.1 (m, 13H), 1.7-2.2 (m, 8H), 1.35/1.3 (d, 3H) (rotámeros).

Ejemplo 85

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 119 (ver el Ejemplo 80), y la amina 56.

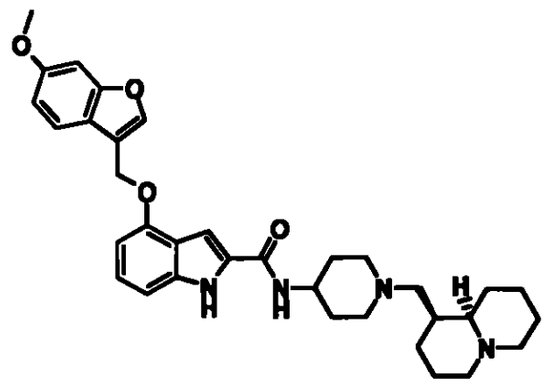
MS (ESI): 575.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.49 (s, 1H), 8.15 (s, 1H), 8.13 (d, 1H), 7.26 (d, 1H), 7.22 (t, 1H), 7.2 (s, 1H), 7.1

411

(t, 1H), 7.02 (d, 1H), 6.97 (d, 1H), 6.71 (d, 1H), 5.34 (s, 2H), 4.43 (d, 1H), 3.95 (s, 3H), 3.72 (m, 1H), 2.6-2.93 (m, 6H), 2.31 (m, 1H), 2.23 (m, 1H), 2.03-2.17 (m, 2H), 1.89 (m, 2H), 1.66-1.77 (m, 3H), 1.42-1.58 (m, 2H), 1.2-1.4 (m, 2H), 0.89 (d, 3H), 0.85 (d, 3H).

Ejemplo 86

{1-[(1s,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (120) (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 108 miligramos (63.8 por ciento). MS (ESI): 571 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.1 (d, 1H), 8.03 (s, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.93 (dd, 1H), 6.7 (d, 1H), 53 (s, 2H), 3.78 (s, 3H), 3.73 (m, 1H), 2.65-2.85 (m, 4H), 2.47 (m, 1H), 2.25 (dd, 1H), 1.2-2.05 (m, 20H).

412

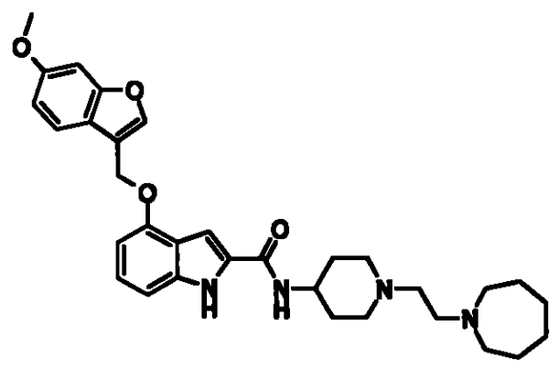
Síntesis del ácido 4-(6-metoxi-benzofuran-3-ilmet xi)-1H-indol-2-carboxílico (120):

Este compuesto se sintetiza a partir del 3-metoxi-fenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55). La ciclación con ácido sulfúrico concentrado (Paso C) dio exclusivamente el benzofurano 6-sustituido.

MS (ESI): 336 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.81 (br s, 1H), 11.71 (s, 1H), 8.02 (s, 1H), 7.56 (d, 1H), 7.18 (s, 1H), 7.13 (dd, 1H), 7.01 (s, 1H), 6.99 (m, 1H), 6.9 (dd, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 3.78 (s, 3H).

Ejemplo 87

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 120 (ver el Ejemplo 86), y la amina 5, de una manera análoga al método descrito en el Ejemplo 1.

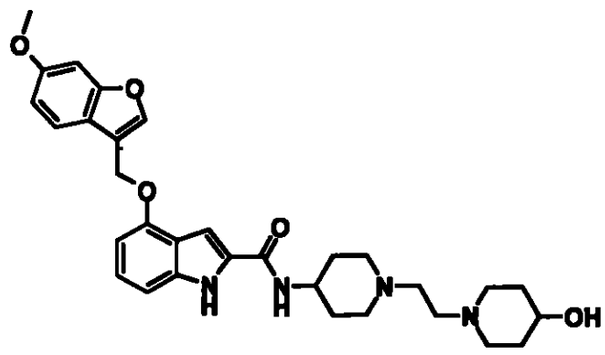
Rendimiento: 121 miligramos (50 por ciento). MS (ESI): 545 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.12 (d, 1H), 8.05 (s, 1H),

413

7.55 (d, 1H), 7.2 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.91 (dd, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 3.8 (s, 3H), 3.7 (m, 1H), 2.85 (m, 2H), 2.5-2.6 (m, 8H), 2.35 (dd, 2H), 2.0 (m, 2H), 1.72 (m, 2H), 1.45-1.6 (m, 8H).

Ejemplo 88

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



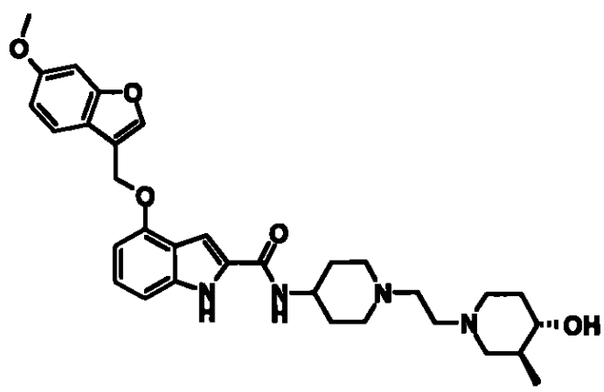
Este compuesto se sintetiza a partir del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 120 (ver el Ejemplo 86), y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 65 miligramos (27 por ciento). MS (ESI): 547 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.1 (br d, 1H), 8.03 (s, 1H), 7.55 (d, 1H), 7.18 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.9 (dd 1H), 6.68 (d, 1H), 5.3 (s, 2H), 45 (br, 1H), 3.78 (s, 3H), 3.72 (m, 1H), 3.4 (m, 1H), 2.9 (m, 2H), 27 (m, 2H), 2.4 (m, 4H), 2.0 (m, 4H), 1.7 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

414
415

Ejemplo 89

Diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



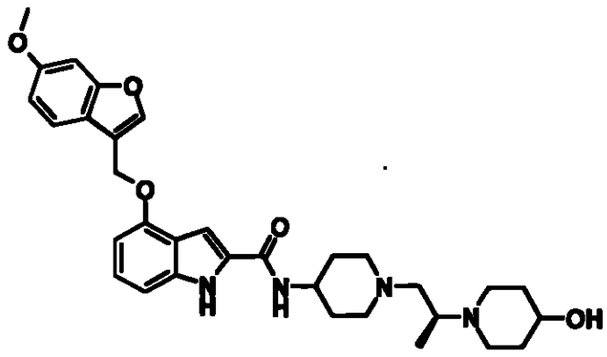
Este compuesto se sintetiza a partir del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 120 (ver el Ejemplo 86), y la amina 14, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 188 miligramos (89 por ciento). MS (ESI): 561 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 8.04 (s, 1H), 7.55 (d, 1H), 7.1-7.3 (m, 3H), 7.0 (d, 1H), 6.9 (dd, 1H), 6.71 (d, 1H), 5.34 (s, 2H), 2.6-4.2 (m, 14H), 1.75-2.2 (m, 8H), 0.93 (d, 3H).

Ejemplo 90

{1-[(S)-2-(4-hidroxi-piperidinil-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílic

415

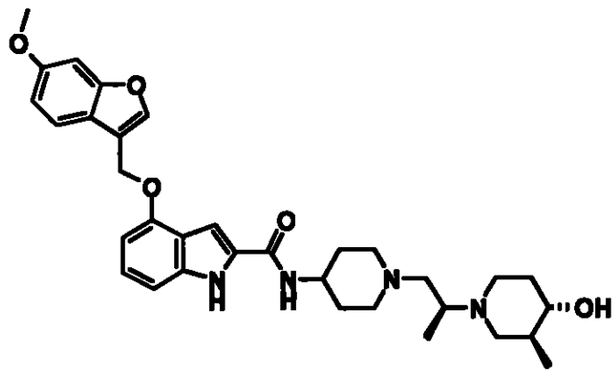


Este compuesto se sintetiza a partir del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 120 (ver el Ejemplo 86), y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 63 miligramos (38 por ciento). MS (ESI): 561 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.18 (d, 1H), 8.04 (s, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.08 (dd, 1H), 7.0 (d, 1H), 6.9 (dd, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.75 (br, 1H), 2.6-4.1 (m, 7H), 0.9-2.4 (m, 20H).

Ejemplo 91

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

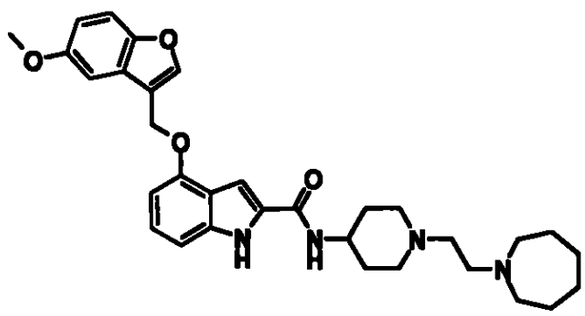


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 120 (ver el Ejemplo 86), y la amina 56.

MS (ESI): 575.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.03 (s, 1H), 7.56 (d, 1H), 7.21 (d, 1H), 7.19 (s, 1H), 7.08 (t, 1H), 7.01 (d, 1H), 6.92 (d, 1H), 6.69 (d, 1H), 5.3 (s, 2H), 3.8 (s, 3H), 3.65-3.8 (m, 1H), 3.31 (m, 2H), 2.59-2.92 (m, 6H), 2.01-2.4 (m, 4H), 1.89 (m, 2H), 1.65-1.78 (m, 3H), 1.19-1.59 (m, 4H), 0.89 (d, 3H), 0.86 (d, 3H).

Ejemplo 92

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (121) (para la preparación, ver más adelante), y la amina 5, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 77 miligramos (48 por ciento). MS (ESI): 545 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.13 (m, 2H), 7.48 (d, 1H), 7.23 (s, 1H), 7.2 (d, 1H), 7.08 (dd, 1H), 7.02 (d, 1H), 6.92 (dd,

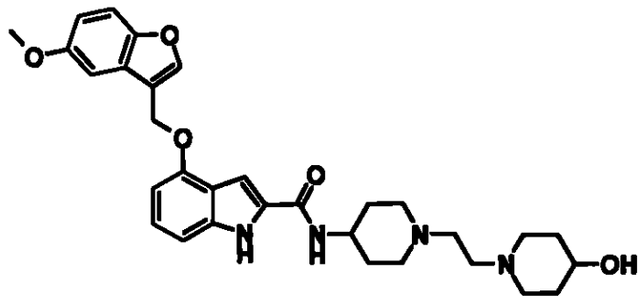
1H), 6.71 (d, 1H), 5.32 (s, 2H), 3.74 (s, 3H), 3.68 (m, 1H), 2.83 (m, 2H), 2.5-2.6 (m, 8H), 2.35 (dd, 2H), 1.98 (dd, 2H), 1.70 (m, 2H), 1.45-16 (m, 8H).

Síntesis del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (121):

Este compuesto se sintetiza a partir de 4-metoxi-fenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55). 460 miligramos (86 por ciento). MS (ESI): 336 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.79 (br s, 1H), 11.73 (s, 1H), 8.1 (s, 1H), 7.46 (d, 1H), 7.22 (d, 1H), 7.15 (dd, 1H), 7.06 (d, 1H), 7.02 (d, 1H), 6.91 (dd, 1H), 6.73 (d, 1H), 5.37 (s, 2H), 3.75 (s, 3H).

Ejemplo 93

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 121 (ver el Ejemplo 92), y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

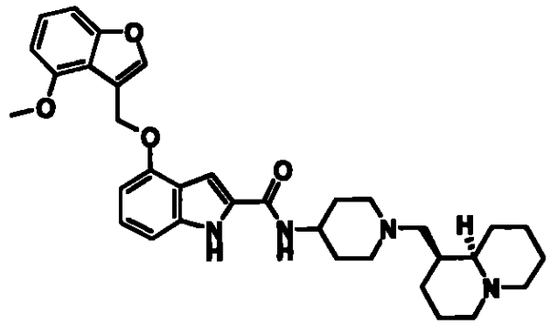
Rendimiento: 105 miligramos (65 por ciento). MS (ESI): 547 $[M+H]^+$,

418
1464

1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.15 (d, 1H), 8.11 (s, 1H), 7.49 (d, 1H), 7.24 (s, 1H), 7.20 (d, 1H), 7.09 (dd, 1H), 7.02 (d, 1H), 6.93 (dd, 1H), 6.71 (d, 1H), 5.33 (s, 2H), 4.51 (br, 1H), 3.75 (s, 3H), 3.7 (m, 1H), 3.41 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.39 (m, 4H), 2.0 (m, 4H), 1.71 (m, 4H), 1.52 (m, 2H), 1.35 (m, 2H).

Ejemplo 94

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (122) (para la preparación, ver más adelante), y 1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-ilamina, 61.

MS (ESI): 571.2 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 7.75 (s, 1H), 7.27 (s, 2H), 7.25 (t, 1H), 7.18 (t, 1H), 7.10 (d, 1H), 7.07 (d, 1H), 6.75 (d, 1H), 6.67 (d, 1H), 5.43 (s, 2H), 4.15 (br s, 1H), 3.4-3.8 (br m, 7H), 3.83 (s, 3H), 2.9-3.25 (m, 4H), 2.53 (br m, 1H), 1.5-2.3 (m, 14H).

Síntesis del ácid 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-

419

carboxílico (122)

(1) 4-metoxi-benzofuran-3-carbaldehído, 123.

A una solución del 4-metoxi-3-metil-benzofurano (*J. Chem. Res. Synopses* (1996), 132) (4 gramos, 24.66 milimoles), en 40 mililitros de dioxano, se le agrega dióxido de selenio (3.39 gramos, 29.59 milimoles), y la mezcla se calienta bajo reflujo durante 24 horas. Luego se enfría y se filtra. El solvente se evapora, y el sólido rojo crudo se utiliza como tal en el siguiente paso.

Rendimiento: 4.86 gramos (>100 por ciento). MS (ESI): 177.0 $[M+H]^+$.

(2) (4-metoxi-benzofuran-3-il)-metanol, 124.

El aldehído 123 anterior (4.34 gramos, 24.63 milimoles) se disuelve en 10 mililitros de metanol, y se enfría en un baño de hielo. Se agrega borohidruro de sodio sólido (4.9 gramos, 123.2 milimoles) en porciones, y la mezcla se agita durante 2 horas. Luego se vierte sobre HCl helado, se extrae tres veces con DCM, se seca, y se evapora. El material crudo se purifica mediante cromatografía sobre gel de sílice utilizando hexano y EtOAc (desde el 20 por ciento hasta el 50 por ciento).

Rendimiento: 1.82 gramos (41 por ciento). MS (ESI): 196.1 $[M+NH_4]^+$.

(3) 2-etil-éster de 1-terbutil-éster del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-indol-1,2-dicarboxílico

Se prepara el indol-éster 125 a partir del alcohol 124 y 102, bajo condiciones de Mitsunobu (como se describe en el Ejemplo 50 para el 105).

MS (ESI): 410.2 $[(M-CMe_3)+H]^+$.

420

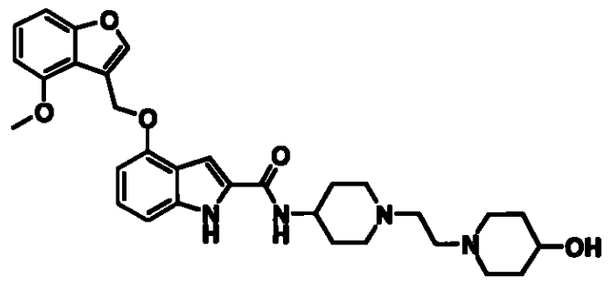
(4) Ácido 4-(4-met xl-benz furan-3-ilmet xl)-1H-indol-2-carboxílico, 122.

El compuesto del título se prepara a partir del éster 125, mediante disociación con KOH/EtOH/THF (como se describe en el Ejemplo 50 para el 105).

MS (ESI): 338.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.76 (s, 1H), 8.07 (s, 1H), 7.29 (t, 1H), 7.21 (s, 1H), 7.19 (t, 1H), 7.1 (s, 1H), 7.04 (d, 1H), 6.83 (d, 1H), 6.69 (d, 1H), 5.39 (s, 2H), 3.84 (s, 3H).

Ejemplo 95

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácid 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



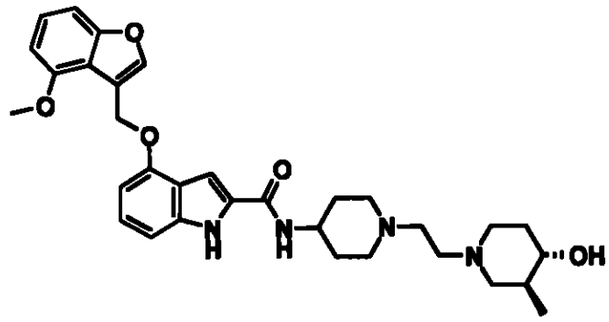
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 122 (ver el Ejemplo 94), y la amina 21.

MS (ESI): 547.2 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 7.63 (s, 1H), 7.13 (s, 1H), 7.12 (t, 1H), 7.04 (t, 1H), 6.98 (d, 1H), 6.94 (d, 1H), 6.62 (d, 1H), 6.53 (d, 1H), 5.3 (s, 2H), 3.76 (m, 1H), 3.71 (s, 3H), 3.54 (m, 1H), 2.85 (m, 2H), 2.73 (m, 2H), 2.42 (m, 4H), 2.07 (m, 4H), 1.81 (m, 2H), 1.74 (m, 2H), 1.53 (m, 2H), 1.45 (m, 2H).

421

Ejemplo 96

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

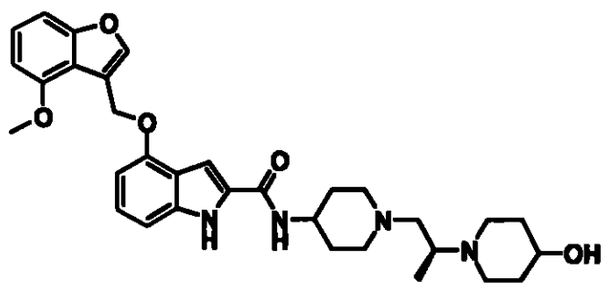


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 122 (ver el Ejemplo 94), y la amina 14.

MS (ESI): 561.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.09 (d, 1H), 8.01 (s, 1H), 7.27 (t, 1H), 7.23 (s, 1H), 7.2 (t, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.81 (d, 1H), 6.65 (d, 1H), 5.34 (s, 2H), 4.47 (d, 1H), 3.79 (s, 3H), 3.7 (m, 1H), 2.64-2.93 (m, 4H), 235 (m, 4H), 1.82-2.05 (m, 3H), 1.63-1.8 (m, 3H), 1.26-1.63 (m, 6H), 0.85 (d, 3H).

Ejemplo 97

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílic



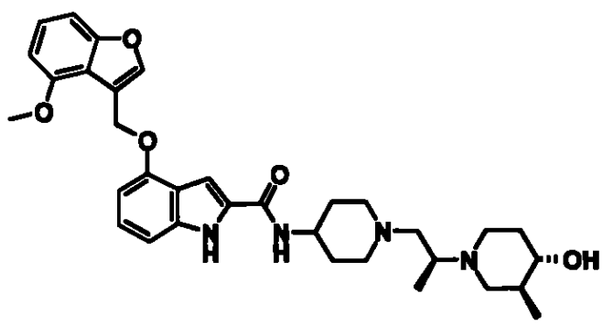
422

Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 122 (ver el Ejemplo 94), y la amina 50.

MS (ESI): 561.2 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 7.62 (s, 1H), 7.13 (s, 1H), 7.12 (t, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.94 (d, 1H), 6.62 (d, 1H), 6.52 (d, 1H), 5.3 (s, 2H), 3.74 (m, 1H), 3.71 (s, 3H), 3.46 (br m, 1H), 2.93 (m, 1H), 2.7 (m, 1H), 2.65-2.75 (m, 3H), 2.4 (m, 1H), 2.28 (m, 2H), 2.12 (m, 2H), 197 (m, 1H), 1.75 (m, 4H), 1.35-1.65 (m, 5H), 0.93 (d, 3H).

Ejemplo 98

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



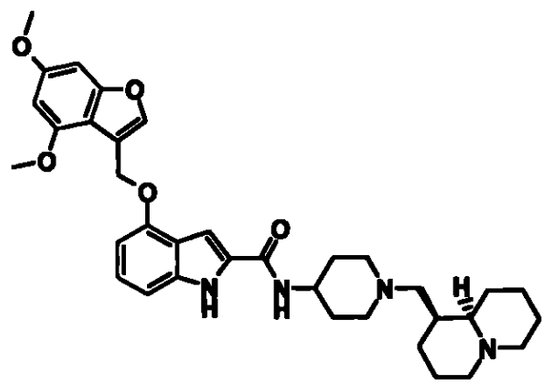
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 122 (ver el Ejemplo 94), y la amina 56.

MS (ESI): 575.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.08 (m, 1H), 8.0 (s, 1H), 7.27 (t, 1H), 7.22 (s, 1H), 7.2 (t, 1H), 7.09 (t, 1H), 7.01 (d, 1H), 6.81 (d, 1H), 6.65 (d, 1H), 5.34 (s, 2H), 4.42 (m,

1H), 3.79 (s, 3H), 3.73 (m, 1H), 2.58-2.92 (m, 6H), 2.31 (m, 1H), 2.22 (m, 1H), 2.02-2.17 (m, 2H), 1.89 (m, 2H), 1.66-1.78 (m, 3H), 1.2-1.6 (m, 4H), 0.9 (d, 3H), 0.86 (d, 3H).

Ejemplo 99

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 126 (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 146 miligramos (76.3 por ciento). MS (ESI): 601 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.1-10.7 (br, 2H), 8.1-8.5 (br, 1H), 7.89 (s, 1H), 7.3 (br s, 1H), 7.1 (dd, 1H), 7.0 (d, 1H), 6.8 (s, 1H), 6.62 (d, 1H), 6.42 (s, 1H), 5.28 (s, 2H), 4.0 (m, 1H), 3.8 (s, 3H), 3.75 (s, 3H), 2.8-3.8 (m, 14H), 1.3-2.1 (m, 12H).

Síntesis del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (126):

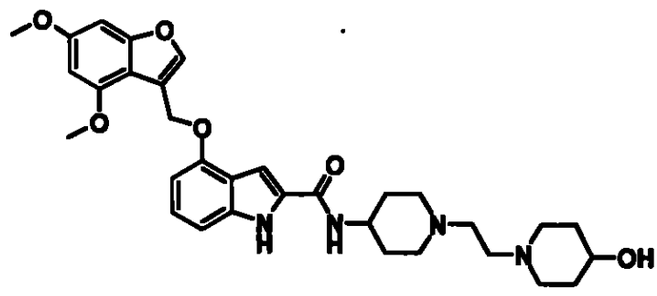
424

Este compuesto se sintetiza a partir de 3,5-dimetoxifenol, de una manera análoga al método descrito para el 106 (ver el Ejemplo 55).

MS (ESI): 366 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.78 (br s, 1H), 11.7 (s, 1H), 7.89 (s, 1H), 7.14 (dd, 1H), 7.08 (d, 1H), 7.02 (d, 1H), 6.78 (d, 1H), 6.65 (d, 1H), 6.41 (d, 1H), 5.31 (s, 2H), 3.79 (s, 3H), 3.31 (s, 3H).

Ejemplo 100

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida de ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



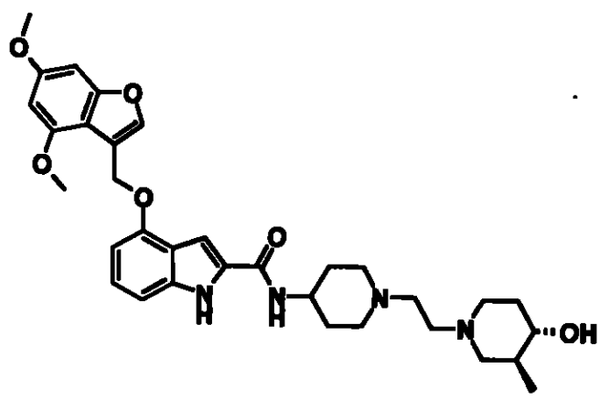
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 126 (ver el Ejemplo 99), y la amina 21.

MS (ESI): 577.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.1 (d, 1H), 7.87 (s, 1H), 7.22 (s, 1H), 7.08 (t 1H), 7.0 (d, 1H), 6.81 (s, 1H), 6.63 (d, 1H), 6.42 (s, 1H), 5.28 (s, 2H), 4.49 (m, 1H), 3.8 (s, 3H), 3.76 (s, 3H), 3.73 (m, 1H), 3.16 (m, 1H), 2.85 (m, 2H), 2.69 (m, 2H), 2.36 (m, 4H), 1.99 (m, 4H), 1.7 (m, 4H), 1.5 (m, 2H), 1.34 (m, 2H).

425

Ejemplo 101

Diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

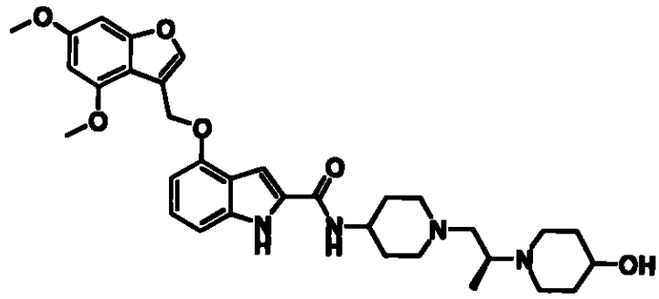


Este compuesto se sintetiza a partir del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 126 (ver eL Ejemplo 99), y la amina 12, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 85 miligramos (47 por ciento). MS (ESI): 591 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 7.87 (s, 1H), 7.25 (s, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.8 (d, 1H), 6.64 (d, 1H), 6.4 (d, 1H), 5.26 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 3.8 (s, 3H), 3.77 (s, 3H), 2.6-3.8 (m, 12H), 1.75-2.2 (m, 8H), 0.93 (d, 3H).

Ejemplo 102

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

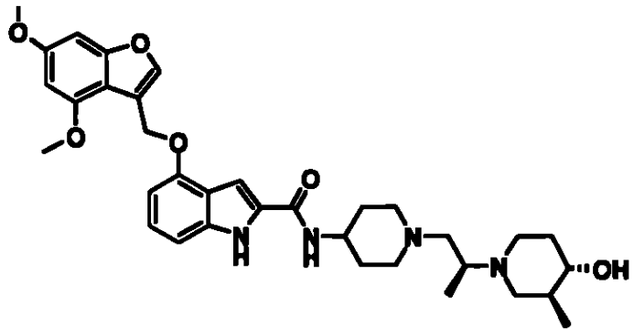


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 126 (ver el Ejemplo 99), y la amina 50.

MS (ESI): 591.3 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 7.63 (s, 1H), 7.23 (s, 1H), 7.14 (t, 1H), 7.04 (d, 1H), 6.67 (s, 1H), 6.62 (d, 1H), 6.37 (s, 1H), 5.35 (d, 2H), 3.85 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.57 (m, 1H), 3.05 (m, 1H), 2.89 (m, 1H), 2.75-2.87 (m, 3H), 2.35-2.55 (m, 3H), 2.24 (m, 2H), 2.08 (m, 1H), 1.8-1.95 (m, 4H), 1.45-1.75 (m, 4H), 1.04 (d, 3H).

Ejemplo 103

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



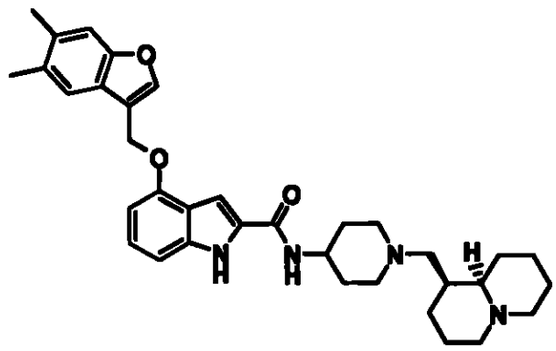
427

Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 126 (ver el Ejemplo 99), y la amina 56.

MS (ESI): 605.1 $[M+H]^+$, 1H-RMN (CD_3OD): δ (ppm) 7.64 (s, 1H), 7.23 (s, 1H), 7.15 (t, 1H), 7.05 (d, 1H), 6.69 (s, 1H), 6.64 (d, 1H), 6.38 (s, 1H), 4.85 (s, 2H), 3.88 (m, 1H), 3.84 (s, 3H), 3.8 (s, 3H), 2.78-3.17 (m, 6H), 2.57 (m, 1H), 2.23-2.47 (m, 3H), 2.03-2.21 (m, 2H), 1.87-1.98 (m, 3H), 1.45-1.8 (m, 4H), 1.08 (d, 3H), 0.99 (d, 3H).

Ejemplo 104

Diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico 127 (para la preparación, ver más adelante), y la amina 61, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 146 miligramos (76.3 por ciento). MS (ESI): 569 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 10.4-10.4 (br, 2H), 8.5 (br, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 7.27 (br s,

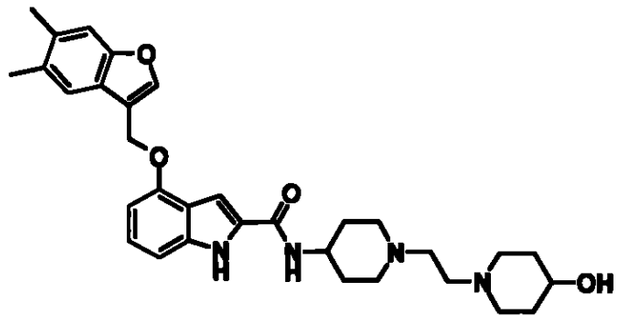
1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 4.0 (m, 1H), 2.8-3.8 (m, 14H), 2.32 (s, 3H), 2.28 (s, 3H), 1.3-2.1 (m, 12H).

Síntesis del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico (127):

Este compuesto se sintetiza a partir de 3,4-dimetilfenol de una manera análoga al método descrito para el 106 (ver el Ejemplo 55). MS (ESI): 334 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.9 (br s, 1H), 11.55 (s, 1H), 8.02 (s, 1H), 7.47 (s, 1H), 7.38 (s, 1H), 7.15 (dd, 1H), 7.0 (m, 2H), 6.7 (d, 1H), 5.3 (s, 2H), 2.35 (s, 3H), 2.3 (s, 3H).

Ejemplo 105

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



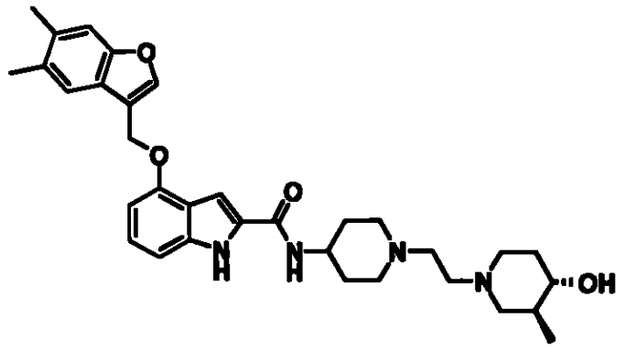
Este compuesto se sintetiza a partir del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 127 (ver el Ejemplo 104), y la amina 21, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 96 miligramos (51 por ciento). MS (ESI): 545.5 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.09 (d, 1H), 8.05 (s, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 7.10 (dd, 1H), 7.0 (d, 1H), 6.88 (s, 1H), 6.7

(d, 1H), 5.28 (s, 2H), 4.45 (d, 1H), 3.7 (m, 1H), 3.38 (m, 1H), 2.84 (m, 2H), 2.7 (m, 2H), 2.5 (s, 3H), 2.38 (s, 3H), 2.35 (m, 4H), 1.95 (m, 4H), 1.7 (m, 4H), 1.45 (m, 2H), 1.3 (m, 2H).

Ejemplo 106

Diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico



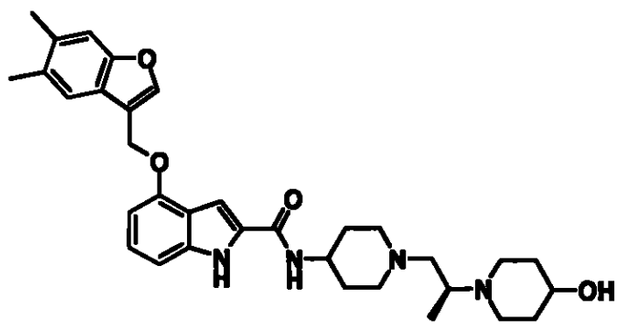
Este compuesto se sintetiza a partir del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 127 (ver el Ejemplo 104), y la amina 14, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 105 miligramos (56 por ciento). MS (ESI): 559 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.6 (br, 2H), 8.5 (d, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 7.4 (s, 1H), 7.25 (d, 1H), 7.1 (dd, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 5.29 (s, 2H), 4.05 (m, 1H), 2.6-3.8 (m, 13H), 2.33 (s, 3H), 2.3 (s, 3H), 1.75-2.2 (m, 8H), 0.93 (d, 3H).

430
127

Ejemplo 107

Diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

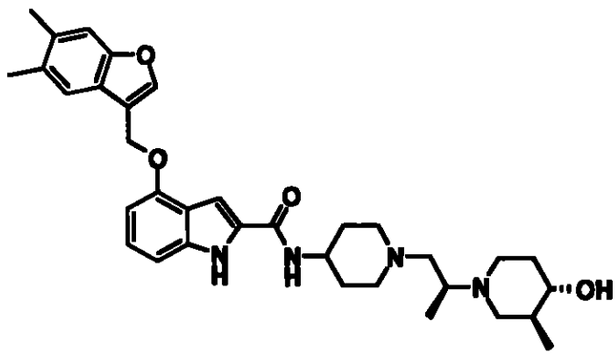


Este compuesto se sintetiza a partir del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 127 (ver el Ejemplo 104), y la amina 50, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 112 miligramos (56.8 por ciento). MS (ESI): 1559 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.3-10.6 (br, 2H), 8.5 (d, 1H), 8.12 (s, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 7.25 (s, 1H), 7.1 (dd, 1H) 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.05 (br, 1H), 2.9-4.1 (m, 13H), 2.35 (s, 3H), 2.28 (s, 3H), 1.7-2.2 (m, 8H), 1.35/1.3 (d, 3H) (isómeros).

Ejemplo 108

Diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmet xi)-1H-indol-2-carboxílic

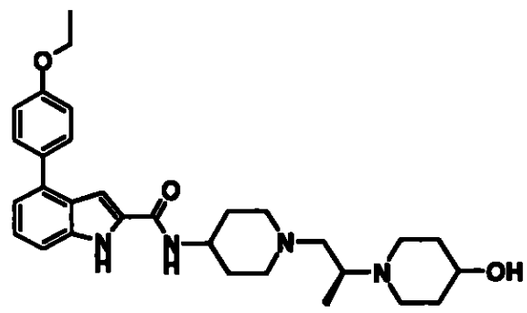


Este compuesto se sintetiza a partir del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico, 127 (ver el Ejemplo 104), y la amina 56, de una manera análoga al método descrito en el Ejemplo 1.

Rendimiento: 130 miligramos (68 por ciento). MS (ESI): 573 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 10.4-10.6 (br, 2H), 8.52 (d, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 7.4 (s, 1H), 7.25 (s, 1H), 7.12 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.3 (s, 2H), 5.1 (br, 1H), 4.05 (m, 1H), 2.8-3.9 (m, 13H), 2.32 (s, 3H), 2.29 (s, 3H), 1.9-21 (m, 6H), 1.32 (d, 3H), 0.93 (d, 3H).

Ejemplo 109

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico

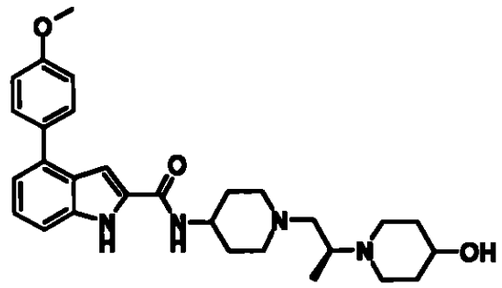


Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir de ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico (preparación de una manera análoga al 128, ver el Ejemplo 141), y la amina 50.

MS (ESI): 505.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.56 (d, 2H), 7.36 (d, 1H), 7.31 (s, 1H), 7.2 (t, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.48 (m, 1H), 4.09 (q, 2H), 3.76 (m, 1H), 3.37 (m, 1H), 2.58-2.96 (m, 5H), 1.85-2.43 (m, 6H), 1.42-1.83 (m, 6H), 1.37 (t, 3H), 1.33 (m, 2H), 0.93 (d, 3H).

Ejemplo 110

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il]-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico



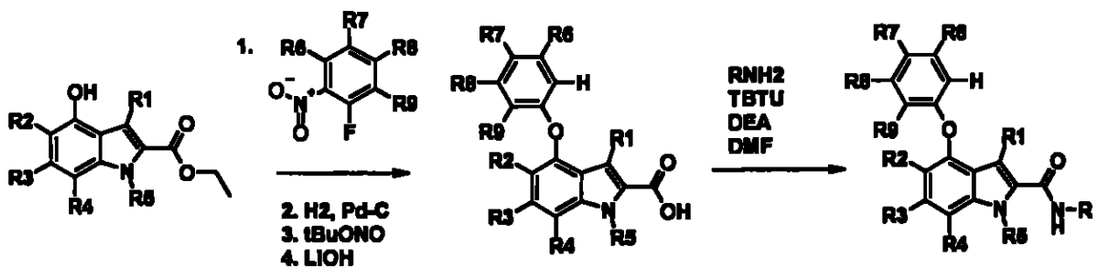
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico 128 (ver el Ejemplo 141), y la amina 50.

MS (ESI): 491 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.59 (s, 1H), 8.23 (d, 1H), 7.56 (d, 2H), 7.34 (d, 1H), 7.31 (s, 1H), 7.2 (t, 1H), 7.06 (d, 2H), 7.01 (d, 1H), 4.44 (d, 1H), 3.81 (s, 3H), 3.75 (m, 1H), 2.96 (m, 1H), 2.6-2.95 (m, 5H), 2.04-2.4 (m, 5H), 1.92 (m, 1H), 1.2-1.85 (m, 8H), 0.91 (d, 3H).

433

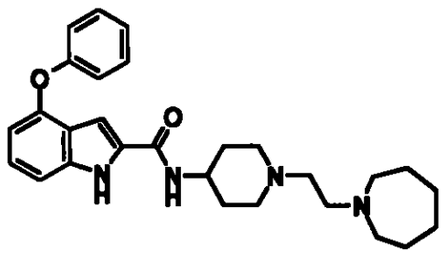
Las 4-ariloxi-indol-2-carboxamidas se preparan en general mediante un acoplamiento de las 4-hidroxi-indol-2-carboxamidas con los 1-fluoro-2-nitro-bencenos correspondientes (Esquema de Reacción 15).

Esquema de Reacción 15:



Ejemplo 111

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-fenoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-fenoxi-1H-indol-2-carboxílico 129 (para la preparación, ver más adelante), y la amina 5.

Rendimiento: 105 miligramos (41 por ciento) de un sólido beige. MS (ESI): 459.4 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.22 (d, 1H), 7.34 (dd, 2H), 7.24 (d, 1H), 7.04-7.15 (m, 3H), 6.95 (d, 2H), 6.55 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.52-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (t, 4H), 1.72 (m, 2H), 1.48 (m, 8H).

434

Síntesis del ácido 4-fenoxi-1H-indol-2-carboxílico (129):

(1) Paso A: Etil-éster del ácido 4-(2-nitro-fenoxi)-1H-indol-2-carboxílico (130).

Se disuelven etil-éster del ácido 4-hidroxi-1H-indol-2-carboxílico (0.5 gramos, 2.436 milimoles), y 2-fluoro-nitro-benceno (0.257 mililitros, 2.436 milimoles) en 10 mililitros de dimetilformamida. Después de la adición de carbonato de potasio (0.67 gramos, 4.87 milimoles), la mezcla se agita durante la noche a la temperatura ambiente. Luego la mezcla de reacción se evapora bajo presión reducida, se disuelve con acetato de etilo, y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo se utiliza en el siguiente paso sin mayor purificación.

Rendimiento: 0.72 gramos (91 por ciento) de un sólido beige. MS (ESI): 325.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 8.1 (d, 1H), 7.6 (dd, 1H), 7.32 (m, 2H), 7.25 (dd, 1H), 7.03 (m, 1H), 6.85 (m, 1H), 6.7 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(2) Paso B: Etil-éster del ácido 4-(2-amino-fenoxi)-1H-indol-2-carboxílico (131).

Se disuelve el 130 (0.5 gramos, 1.532 milimoles) en 100 mililitros de etanol, y después de la adición de Pd-C (100 miligramos), la mezcla se hidrogena a temperatura ambiente durante 3 horas. La mezcla se filtra sobre Celite, para remover el catalizador, y se evapora.

Rendimiento: 390 miligramos (86 por ciento) de un sólido gris. MS

435

(ESI): 297 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.95 (s, 1H), 7.13 (m, 2H), 7.0 (s, 1H), 6.88 (m, 1H), 6.8 (dd, 1H), 6.75 (dd, 1H), 6.5 (m, 1H), 6.38 (m, 1H), 4.9 (br, 2H), 4.3 (q, 2H), 1.3 (t, 3H).

(3) Paso C: Etil-éster del ácido 4-fenoxi-1H-indol-2-carboxílico (132).

Se disuelve nitrito de terbutilo (0.2 mililitros, 1.687 milimoles) en 5 mililitros de dimetilformamida, y se calienta a 65°C. Se agrega por goteo una solución del 131 (0.5 gramos, 1.687 milimoles) en 5 mililitros de dimetilformamida, y la mezcla se agita durante 10 minutos adicionales. La solución castaña se enfría a temperatura ambiente, y se diluye con dietiléter, y se lava con HCl 2N y salmuera. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo (370 miligramos de un aceite castaño) se purifica adicionalmente mediante cromatografía por evaporación (hexano/acetato de etilo, 9:1).

Rendimiento: 163 miligramos (34 por ciento) de un sólido amarillo. MS (ESI): 280.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.05 (s, 1H), 7.37 (d, 1H), 7.35 (d, 1H), 7.23 (m, 2H), 7.1 (dd, 1H), 7.0 (d, 2H), 6.82 (s, 1H), 6.6 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Paso D: Ácido 4-fenoxi-1H-indol-2-carboxílico (129).

Se disuelve el 132 (160 miligramos, 0.569 milimoles) en 5 mililitros de metanol, y se trata con una solución de LiOH (27.2 miligramos, 1.138 milimoles) en 3 mililitros de agua. La mezcla se agita a temperatura ambiente durante la noche. Debido a que la reacción no está completa, cromatografía de capa delgada), se

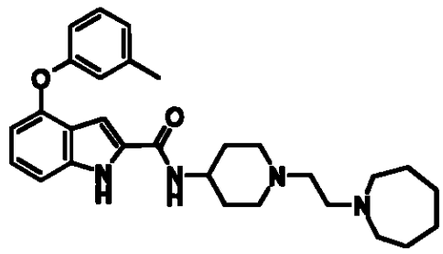
436

agrega LiOH adicional (30 miligramos, 1.25 milimoles), y se continúa la agitación durante 18 horas adicionales. Después de la evaporación, el producto crudo se acidifica a 0°C con HCl 2M, y se extrae con acetato de etilo. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan.

Rendimiento: 146 miligramos (100 por ciento) de un sólido amarillo; MS (ESI): 253 [M]+, 1H-RMN (DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.9 (s, 1H), 7.38 (d, 1H), 7.34 (d, 1H), 7.2 (m, 2H), 7.12 (m, 1H), 7.0 (d, 2H), 6.75 (s, 1H), 6.58 (d, 1H).

Ejemplo 112

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-m-toliloxi-1H-indol-2-carboxílico 133 (para la preparación, ver más adelante), y la amina 5.

Rendimiento: 12 miligramos (11.3 por ciento) de un sólido blanco; MS (ESI): 473.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.2 (d, 1H), 7.2 (m, 2H), 7.1 (m, 2H), 6.88 (d, 1H), 6.78 (m, 1H), 6.7 (m, 1H), 6.54 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.48-2.58 (m, 8H), 2.35 (m, 2H), 2.25 (s, 3H), 1.98 (m, 2H), 1.75 (m, 2H), 1.48-1.55 (m,

437

8H).

Síntesis del ácido 4-m-toliloxi-1H-indol-2-carboxílico (133):

(1) Paso A: Etiléster del ácido 4-(5-metil-2-nitro-fenoxi)-1H-indol-2-carboxílico (134).

Se disuelven etiléster del ácido 4-hidroxi-1H-indol-2-carboxílico (1 gramo, 4.87 milimoles) y 2-fluoro-4-metil-1-nitro-benceno (756 miligramos, 4.87 milimoles) en 20 mililitros de dimetilformamida. Después de la adición de carbonato de potasio (1.3 gramos, 9.74 milimoles), la mezcla se agita durante la noche a temperatura ambiente. Luego la mezcla de reacción se evapora bajo presión reducida, se disuelve con acetato de etilo, y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo se utiliza en el siguiente paso sin mayor purificación. Rendimiento: 1.59 gramos (96 por ciento) de un sólido beige. MS (ESI): 341 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 7.98 (d, 1H), 7.3 (d, 1H), 7.25 (dd, 1H), 7.15 (d, 1H), 6.88 (d, 1H), 6.63 (d, 1H), 43 (q, 2H), 2.28 (s, 3H), 13 (t, 3H).

(2) Paso B: Etiléster del ácido 4-(2-amino-5-metil-fenoxi)-1H-indol-2-carboxílico (135).

Se disuelve el 134 (1.3 gramos, 3.82 milimoles) en 250 mililitros de acetato de etilo, y, después de la adición de Pd-C (200 miligramos), la mezcla se hidrogena a temperatura ambiente durante 2 horas. La mezcla se filtra sobre Celite, para remover el catalizador, y se evapora.

Rendimiento: 1.12 gramos (95 por ciento) de un sólido gris. MS

438
+434

(ESI): 311 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.95 (br, 1H), 7.13 (m, 2H), 7.03 (s, 1H), 6.72 (s, 2H), 6.58 (s, 1H), 6.37 (m, 1H), 4.68 (br, 2H), 4.3 (q, 2H), 2.08 (s, 3H), 1.3 (t, 3H).

(3) Paso C: Etiléster del ácido 4-m-toliloxi-1H-indol-2-carboxílico (136)

Se disuelve nitrito de terbutilo (0.428 mililitros, 3.609 milimoles) en 5 mililitros de dimetilformamida, y se calienta a 65°C. Se agrega por goteo una solución del 135 (1.1 gramos, 3.609 milimoles) en 5 mililitros de dimetilformamida, y la mezcla se agita durante 10 minutos adicionales. La solución castaña se enfría a temperatura ambiente, se diluye con dietil-éter, y se lava con HCl 2N y salmuera. Las capas orgánicas se secan sobre sulfato de sodio, y se evaporan. El producto crudo (930 gramos de un aceite castaño) se purifica adicionalmente mediante cromatografía por evaporación (hexano/acetato de etilo, 7:3).

Rendimiento: 520 miligramos (49 por ciento) de un sólido amarillo; MS (ESI): 294.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.0 (s, 1H), 7.18 - 7.24 (m, 3H), 6.92 (m, 1H), 6.82 (m, 2H), 6.78 (dd, 1H), 6.58 (dd, 1H), 4.28 (q, 2H), 2.27 (s, 3H), 1.3 (t, 3H).

(4) Paso D: Ácido 4-m-tolíloxi-1H-indol-2-carboxílico (133).

Se disuelve al 136 (520 miligramos, 1.761 milimoles) en 10 mililitros de metanol, y se trata con una solución de LiOH (84.3 miligramos, 3.52 milimoles) en 5 mililitros de agua. La mezcla se agita a temperatura ambiente durante 18 horas. Después de la evaporación, el producto crudo se acidifica a 0°C con HCl 2M, y se

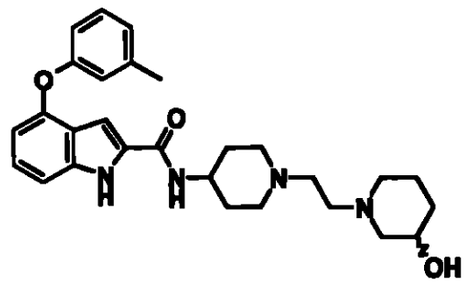
439

extrae con acetato de etilo. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan.

Rendimiento: 460 miligramos (98 por ciento) de un sólido beige; MS (ESI): 266.1 $[M-H]^-$, 1H-RMN (DMSO-d_6: δ (ppm) 12.9 (s, 1H), 11.9 (s, 1H), 7.15 - 7.25 (m, 3H), 6.9 (m, 1H), 6.84 (m, 1H), 6.78 (m, 2H), 6.57 (m, 1H), 2.27 (s, 3H).

Ejemplo 113

{1-[2-(3-(RS)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico.



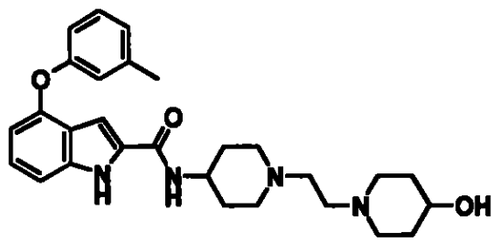
Este compuesto se sintetiza de una manera análoga al Ejemplo 1 a partir del ácido 4-m-toliloxi-1H-indol-2-carboxílico 133 (ver el Ejemplo 112) y la amina racémica 12.

Rendimiento: 34 miligramos (21 por ciento) de un sólido amarillo; MS (ESI): 477.3 $[M+H]^+$, 1H-RMN (80°C, DMSO-d_6): δ (ppm) 11.2 (s, 1H), 7.77 (d, 1H), 7.24 (dd, 1H), 7.2 (dd, 1H), 7.1 (ss, 1H), 7.04 (s, 1H), 6.88 (d, 1H), 6.8 (m, 1H), 6.75 (m, 1H), 6.54 (d, 1H), 3.75 (m, 1H), 3.5 (m, 1H), 2.7 - 2.9 (m, 4H), 2.6 (m, 1H), 2.44 (m, 4H), 2.3 (s, 3H), 2.13 (m, 2H), 2.05 (m, 1H), 1.95 (m, 1H), 1.7 - 1.85 (m, 3H), 1.55 - 1.65 (m, 3H), 1.4 (m, 1H), 1.15 (m, 1H).

440

Ejemplo 114

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico.



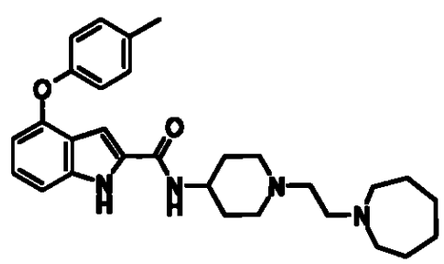
Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-m-toliloxi-1H-indol-2-carboxílico 133 (ver el Ejemplo 112), y la amina 21.

Rendimiento: 45 miligramos (28 por ciento) de un sólido blanco;

MS (ESI): 477 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.2 (m, 2H), 7.1 (m, 2H), 6.88 (d, 1H), 6.78 (m, 1H), 6.7 (m, 1H), 6.54 (d, 1H), 4.47 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.38 (m, 4H), 2.28 (s, 3H), 1.98 (m, 4H), 1.63 - 1.75 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Ejemplo 115

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico.



441

Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-p-toliloxi-1H-indol-2-carboxílico 137 (para la preparación, ver más adelante), y la amina 5.

Rendimiento: 12 miligramos (11.3 por ciento) de un sólido blanco; MS (ESI): 473.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.18 (d, 1H), 7.05 - 7.2 (m, 5H), 6.85 (d, 2H), 6.47 (m, 1H), 3.7 (m, 1H), 2.85 (m, 2H), 2.47 - 2.58 (m, 6H), 2.35 (m, 2H), 2.25 (s, 3H), 1.98 (m, 2H), 1.75 (m, 2H), 1.48 - 1.55 (m, 10H).

Síntesis del ácido 4-p-toliloxi-1H-indol-2-carboxílico (137):

(1) Paso A: Etil-éster del ácido 4-(3,5-difluoro-2-nitro-fenoxi)-1H-indol-2-carboxílico (138).

Se disuelven etil-éster del ácido 4-hidroxi-1H-indol-2-carboxílico (1 gramo, 4.87 milimoles) y 1-fluoro-4-metil-2-nitro-benceno (0.6 mililitros, 4.87 milimoles) en 10 mililitros de dimetil-formamida. Después de la adición de carbonato de potasio (1.3 gramos, 9.74 milimoles), la mezcla se agita durante la noche a temperatura ambiente. Luego la mezcla de reacción se evapora bajo presión reducida, se disuelve con acetato de etilo, y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio, y se evaporan. El producto crudo (1.51 gramos de un aceite castaño) se purifica adicionalmente mediante cromatografía por evaporación (hexano / acetato de etilo, 9:1).

Rendimiento: 570 miligramos (34 por ciento) de un sólido blanco. MS (ESI): 341 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.88 (d, 1H), 7.45 (dd, 1H), 7.27 (d, 1H), 7.22 (dd, 1H), 6.98 (d, 1H), 6.87 (s,

442
HHB

1H), 6.6 (d, 1H), 4.3 (q, 2H), 2.35 (s, 3H), 1.3 (t, 3H).

(2) Paso B: Etil-éster del ácido 4-(2-amino-4-metil-fenoxi)-1H-indol-2-carboxílico (139).

Se disuelve el 138 (570 miligramos, 1.675 milimoles) en 150 mililitros de etanol, y, después de la adición de Pd-C (200 miligramos), la mezcla se hidrogena a temperatura ambiente durante 2 horas. La mezcla se filtra sobre Celite para remover el catalizador, y se evapora.

Rendimiento: 3.08 gramos (100 por ciento) de un aceite castaño. MS (ESI): 311 $[M+H]^+$.

(3) Paso C: Etil-éster del ácido 4-p-toliloxi-1H-indol-2-carboxílico (140).

Se disuelve nitrito de terbutilo (0.176 mililitros, 1.48 milimoles) en 5 mililitros de dimetil-formamida, y se calienta a 65°C. Se agrega por goteo una solución del 139 (460 miligramos, 1.48 milimoles) en 5 mililitros de dimetil-formamida, y la mezcla se agita durante 10 minutos adicionales. La solución castaña se enfría a temperatura ambiente, se diluye con dietil-éter, y se lava con HCl 2N y salmuera. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo (420 miligramos de un aceite castaño) se purifica adicionalmente mediante cromatografía por evaporación (hexano / acetato de etilo, 9:1).

Rendimiento: 70 miligramos (16 por ciento) de un sólido amarillo; MS (ESI) 294.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.0 (s, 1H), 7.15-7.24 (m, 4H), 7.4 (m, 2H), 6.85 (d, 1H), 6.52 (dd, 1H), 4.3 (q, 2H),

443

2.28 (s, 3H), 1.3 (t, 3H).

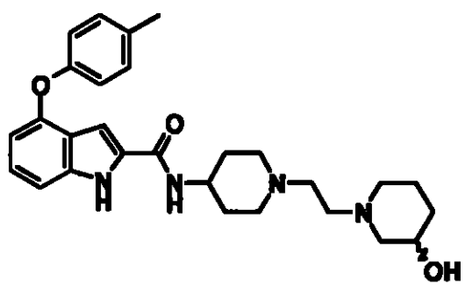
(4) Paso D: Ácido 4-p-toliloxi-1H-indol-2-carboxílico (137)

Se disuelve el 140 (70 miligramos, 0.237 milimoles) en 5 mililitros de metanol y se trata con una solución de LiOH (11.4 miligramos, 0.474 milimoles) en 3 mililitros de agua. La mezcla se agita a temperatura ambiente durante 18 horas. Después de la evaporación, el producto crudo se acidifica a 0°C con HCl 2M, y se extrae con acetato de etilo. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan.

Rendimiento: 60 miligramos (100 por ciento) de un sólido beige; MS (ESI) 266.2 $[M-H]^-$, 1H-RMN (^{1}DMSO-d_6): δ (ppm) 12.9 (s, 1H), 11.8 (s, 1H), 7.13-7.2 (m, 4H), 6.9 (m, 2H), 6.77 (d, 1H), 6.52 (dd, 1H), 2.29 (s, 3H).

Ejemplo 116

{1-[2-(3-(RS)-hidroxi-piperidin-1-il)-etil-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico



Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir del ácido 4-p-toliloxi-1H-indol-2-carboxílico 137 (ver Ejemplo 115) y la amina racémica 12.

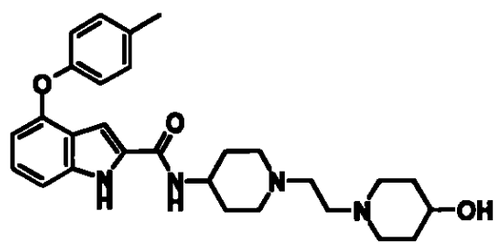
Rendimiento: 87 miligramos (49 por ciento) de un sólido beige; MS

444

(ESI) 475.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.2 (d, 1H), 7.08-7.2 (m, 5H), 6.87 (s, 2H), 6.47 (d, 1H), 4.53 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 3H), 2.65 (m, 1H), 2.37 (m, 4H), 2.28 (s, 3H), 1.98 (t, 2H), 1.7-1.85 (m, 5H), 1.55 (m, 3H), 1.35 (m, 1H), 1.05 (m, 1H).

Ejemplo 117:

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico



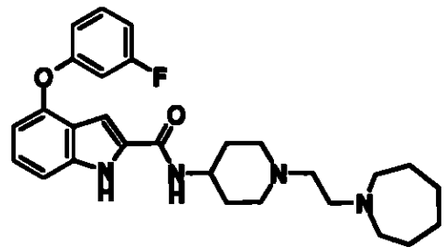
Este compuesto se sintetiza de manera análoga al Ejemplo 1 a partir del ácido 4-p-toliloxi-1H-indol-2-carboxílico 137 (ver, Ejemplo 115) y la amina 21.

Rendimiento: 80 miligramos (45 por ciento) de un sólido beige; MS (ESI) 475.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.2 (d, 1H), 7.07-7.2 (m, 5H), 6.85 (d, 2H), 6.47 (d, 1H), 4.48 (br, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.35 (m, 4H), 2.27 (s, 3H), 195-2.05 (m, 4H), 1.65-1.75 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Ejemplo 118

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3-fluoro-fenoxi)-1H-ind l-2-carboxílico

445



Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir del ácido 4-(3-fluoro-fenoxi)-1H-indol-2-carboxílico 141 (para la preparación, ver más adelante) y la amina 5.

Rendimiento: 50 miligramos (28.3 por ciento) de un sólido blanco; MS (ESI) 479.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.2 (d, 1H), 7.35 (dd, 1H), 7.28 (d, 1H), 7.18 (dd, 1H), 7.05 (s, 1H), 6.9 (dd, 1H), 6.73-6.8 (m, 2H), 6.68 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.5-2.58 (m, 6H), 2.35 (m, 2H), 1.98 (m, 2H), 1.72 (m, 2H), 1.48-1.55 (m, 10H).

Síntesis del ácido 4-p-tolilioxi-1H-indol-2-carboxílico (141):

(1) Paso A: Etil-éster del ácido 4-(3,5-difluoro-2-nitro-fen xi)-1H-indol-2-carboxílico (142)

Se disuelven el etil-éster del ácido 4-hidroxi-1H-indol-2-carboxílico (1 gramo, 4.87 milimoles) y 2,4-difluoro-1-nitro-benceno (0.534 mililitros, 4.87 milimoles) en 20 mililitros de dimetilformamida. Después de la adición de carbonato de potasio (1.3 gramos, 9.74 milimoles), la mezcla se agita durante la noche a temperatura ambiente. Luego la mezcla de reacción se evapora bajo presión reducida, se siduelve con acetato de etilo y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El

446

producto crudo se utiliza en el siguiente paso sin mayor purificación. Rendimiento: 1.63 gramos (97 por ciento) de una resina gris; MS (ESI):343.1 $[M-H]^-$.

(2) Paso B: Etil-éster del ácido 4,4-(2-amino-5-fluoro-fenoxi)-1H-Indol-2-carboxílico (143)

Se disuelve el 142 (1.6 gramos, 4.734 milimoles) en 250 mililitros de acetato de etilo y, después de la adición de Pd-C (200 miligramos), la mezcla se hidrogena a temperatura ambiente durante 2 horas. La mezcla se filtra sobre Celite para remover el catalizador y se evapora.

Rendimiento: 1.41 gramos (95 por ciento) de una espuma gris. MS (ESI): 315.2 $[M+H]^+$.

(3) Paso C: Etil-éster del ácido 4-(3-fluoro-fenoxi)-1H-Indol-2-carboxílico (144)

Se disuelve nitrito de tert-butilo (0.46 mililitros, 4.45 milimoles) en 5 mililitros de dimetilformamida y se calienta a 65°C. Se agrega por goteo una solución de 143 (1.4 gramos, 4.45 milimoles) en 5 mililitros de dimetilformamida y la mezcla se agita durante 10 minutos adicionales. La solución café se enfría a temperatura ambiente, se diluye con dietil-éter y se lava con HCl 2N y salmuera. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo (1.0 gramos de un aceite café) se purifica además mediante cromatografía por evaporación (hexano / acetato de etilo 7:3).

Rendimiento: 440 miligramos (33 por ciento) de un sólido amarillo;

MS (ESI) 298.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.35 (dd, 1H), 7.3 (d, 1H), 7.25 (dd, 1H), 6.92 (dd, 1H), 6.77-6.87 (m, 3H), 6.7 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

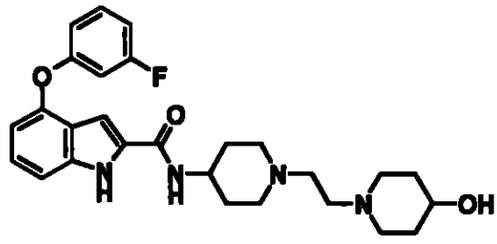
(4) Paso D: Ácido 4-(3-fluoro-fenoxi)-1H-indol-2-carboxílic (141)

El 144 (440 miligramos, 1.47 milimoles) se disuelve en 10 mililitros de metanol y se trata con una solución de LiOH (70 miligramos, 1.47 milimoles) en 5 mililitros de agua. La mezcla se agita a temperatura ambiente durante 18 horas. Después de la evaporación, el producto crudo se acidifica a 0°C con HCl 2M y se extrae con acetato de etilo. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan.

Rendimiento: 420 miligramos (100 por ciento) de un sólido amarillo; MS (ESI): 270.1 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.95 (s, 1H), 11.9 (s, 1H), 7.35 (dd, 1H), 7.28 (dd, 1H), 6.9 (dd, 1H), 6.77-6.85 (m, 2H), 5.75 (s, 1H), 6.7 (d, 1H).

Ejemplo 119

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3-fluoro-fenoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir del ácido 4-(3-fluoro-fenoxi)-1H-indol-2-carboxílico 141 (ver

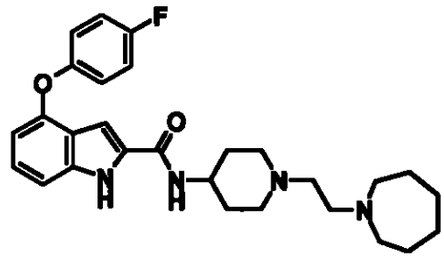
448

ejemplo 118) y la amina 21.

Rendimiento: 35 miligramos (20 por ciento) de un sólido blanco; MS (ESI): 479 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.21 (d, 1H), 7.35 (dd, 1H), 7.29 (d, 1H), 7.18 (dd, 1H), 7.05 (s, 1H), 6.9 (dd, 1H), 6.73-6.8 (m, 2H), 6.68 (d, 1H), 4.49 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.37 (m, 4H), 1.95 (m, 4H), 1.63-1.77 (m, 4H), 1.5 (m, 2H), 1.35 (m, 2H).

Ejemplo 120

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(fluoro-fenoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico 145 (para la preparación, ver más adelante) y la amina 5.

Rendimiento: 86 miligramos (49 por ciento) de un sólido blanco; MS (ESI): 477.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 1.75 (s, 1H), 8.2 (d, 1H), 7.14-7.24 (m, 5H), 7.0 (m, 2H), 6.5 (d, 1H), 3.72 (m, 1H), 2.85 (m, 2H), 2.5-2.6 (m, 6H), 2.36 (m, 2H), 1.98 (m, 2H), 1.72 (m, 2H), 1.48-1.57 (m, 10H).

Síntesis del ácido 4-p-toliloxi-1H-indol-2-carboxílico (145):

(1) Paso A: Etil-éster del ácido 4-(4-fluor -2-nitro-fenoxi)-1H-

449

Indol-2-carb xílico (146)

Se disuelven el etil-éster del ácido 4-hidroxi-1H-indol-2-carboxílico (0.92 gramos, 4.483 milimoles) y 1,4-difluoro-2-nitro-benceno (0.486 mililitros, 4.483 milimoles) en 10 mililitros de dimetilformamida. Después de la adición de carbonato de potasio (1.2 gramos, 8.96 milimoles), la mezcla se agita durante la noche a temperatura ambiente. Luego, la mezcla de reacción se evapora bajo presión reducida, se disuelve con acetato de etilo y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo se utiliza en el siguiente paso sin mayor purificación.

Rendimiento: 1.45 gramos (94 por ciento) de una resina gris; MS (ESI): 343.1 $[M-H]^-$-, 1H-RMN (DMSO-d_6): δ (ppm) 12.15 (s, 1H), 8.08 (m, 1H), 7.55 (m, 1H), 7.3 (d, 1H), 7.24 (dd, 1H), 7.15 (dd, 1H), 6.9 (s, 1H), 6.62 (d, 1H), 4.3 (q, 2H) 1.32 (t, 3H).

(2) Paso B: Etil-éster del ácido 4-(2-amino-4-fluoro-fenoxi)-1H-indol-2-carboxílico (147)

El **146** (1.5 gramos, 4.21 milimoles) se disuelve en 200 mililitros de acetato de etilo y, después de la adición de Pd-C (200 miligramos), la mezcla se hidrogena a temperatura ambiente durante 2 horas. La mezcla se filtra sobre Celite para remover el catalizador y se evapora.

Rendimiento: 1.31 gramos (99 por ciento) de un sólido beige; MS (ESI): 313.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.95 (s, 1H), 7.12 (m, 2H), 7.05 (m, 1H), 6.75 (dd, 1H), 6.58 (dd, 1H), 6.34 (m, 1H),

450
#51

6.28 (dt, 1H), 5.25 (br, 2H), 4.3 (q, 2H), 1.32 (t, 3H).

(3) Paso C: Etil-éster del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico (148)

Se disuelve nitrito de tert-butilo (0.46 mililitros, 4.45 milimoles) en 5 mililitros de dimetilformamida y se calienta a 65°C. Se agrega por goteo una solución del 147 (1.4 gramos, 4.45 milimoles) en 5 mililitros de dimetilformamida y la mezcla se agita 10 minutos adicionales. La solución café se enfría a temperatura ambiente, se diluye con dietil-éter y se lava con HCl 2N y salmuera. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo (1.0 gramos de un aceite café) se purifica adicionalmente mediante cromatografía por evaporación (hexano / acetato de etilo 7:3).

Rendimiento: 440 miligramos (33 por ciento) de un sólido amarillo; MS (ESI): 298.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.05 (s, 1H), 7.2 (m, 4H), 7.05 (m, 2H), 6.85 (m, 1H), 6.54 (d, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Paso D: Ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico (145)

El 148 (510 miligramos, 1.7 milimoles) se disuelve en 10 mililitros de metanol y se trata con una solución de LiOH (82 miligramos, 3.4 milimoles) en 5 mililitros de agua. La mezcla se agita a temperatura ambiente durante 18 horas. Después de la evaporación, el producto crudo se acidifica a 0°C con HCl 2M y se extrae con acetato de etilo. Las capas orgánicas se secan sobre

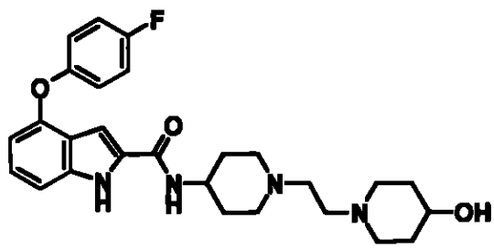
4151

sulfato de sodio y se evaporan.

Rendimiento: 460 miligramos (100 por ciento) de un sólido amarillo; MS (ESI): 270.1 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 13.0 (s, 1H), 11.9 (s, H), 7.15-7.22 (m, 4H), 7.05 (m, 2H), 6.78 (m, 1H), 6.55 (d, 1H).

Ejemplo 121

{1-[2-(-4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico



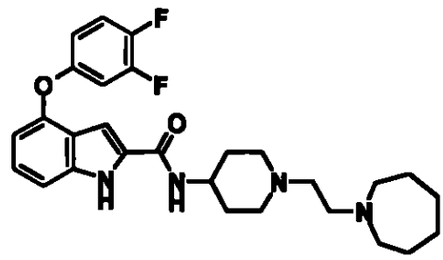
Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico **145** (ver ejemplo **120**) y la amina **21**.

Rendimiento: 66 miligramos (37 por ciento) de un sólido blanco; MS (ESI): 479 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.1-7.24 (m, 5H), 7.0 (m, 2H), 6.5 (d, 1H), 4.46 (br, 1H), 3.72 (m, 1H), 3.42 (m, 1H), 2.85 (m, 2H), 2.7 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.64-1.77 (m, 4H), 1.53 (m, 2H), 1.35 (m, 2H).

Ejemplo 122

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,4-dicloro-fenoxi)-1H-indol-2-carboxílic

452



Este compuesto se sintetiza de manera análiga al Ejemplo 1, a partir del ácido 4-(3,4-difluoro-fenoxi)-1H-indol-2-carboxílico 149 (para la preparación, ver más adelante) y la amina 6.

Rendimiento: 62 miligramos (36 por ciento) de un sólido blanco; MS (ESI): 495.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.23 (d, 1H), 7.44 (m, 1H), 7.26 (d, 1H), 7.14 (m, 1H), 7.0 (m, 1H), 6.80 (m, 1H), 6.56 (d, 2H), 3.72 (m, 1H), 2.87 (m, 2H), 2.5-2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47-1.55 (m, 10H).

Síntesis del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico (149):

(1) Paso A: Etil-éster del ácido 4-(3,5-difluoro-2-nitro-fenoxi)-1H-indol-2-carboxílico (150)

Se disuelven el etil-éster del ácido 4-hidroxi-1H-indol-2-carboxílico (1 gramo, 4.87 milimoles) y 1,2,4-trifluoro-5-nitro-benceno (0.559 mililitros, 4.87 milimoles en 10 mililitros de dimetilformamida. Después de adicionar carbonato de potasio (1.3 gramos, 9.74 milimoles) la mezcla se agita durante la noche a temperatura ambiente. Luego, la mezcla de reacción se evapora bajo presión reducida, se disuelve con acetato de etilo y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio y se

453

evaporan.

Rendimiento: 1.79 gramos (100 por ciento) de una espuma amarilla; MS (ESI): 361.1 $[M-H]^-$.

(2) Paso B: Etil-éster del ácido 4-(2-amino-4,5-difluoro-fenoxi)-1H-indol-2-carboxílico (151)

El 150 (1.8 gramos, 4.87 milimoles) se disuelve en 150 mililitros de acetato de etilo y, después de la adición de Pd-C (500 miligramos), la mezcla se hidrogena a temperatura ambiente durante 2 horas. La mezcla se filtra sobre Celite para remover el catalizador y se evapora.

Rendimiento: 1.61 gramos (99 por ciento) de una espuma café; MS (ESI): 333.2 $[M+H]^+$.

(3) Paso C: Etil-éster del ácido 4-(3,4-difluoro-fenoxi)-1H-indol-2-carboxílico (152)

Se disuelve nitrito de tert-butilo (0.575 mililitros, 4.85 milimoles) en 5 mililitros de dimetilformamida y se calienta a 65°C. Se agrega por goteo una solución de 151 (1.6 gramos, 4.85 milimoles) en 5 mililitros de dimetilformamida y la mezcla se agita durante 10 minutos adicionales. La solución café se enfría a temperatura ambiente, se diluye con dietil-éter y se lava con HCl 2N y salmuera. Las capas orgánicas se secan sobre sulfato de sodio y se evapora. El producto crudo (1.78 gramos de un aceite café) se purifica adicionalmente mediante cromatografía por evaporación (hexano / acetato de etilo 9:1).

Rendimiento: 380 miligramos (25 por ciento) de un sólido ligeramente

454

amarillo; MS (ESI): 316.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.1 (s, 1H), 7.45 (m, 1H), 7.27 (d, 1H), 7.2 (dd, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 6.95 (m, 1H), 6.55 (d, 1H), 4.3 (q, 2H), 1.34 (t, 3H).

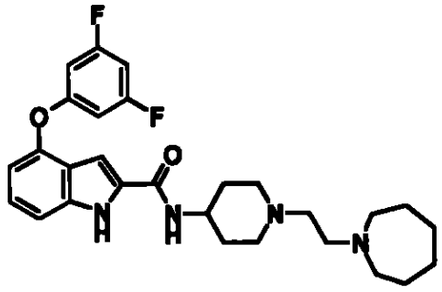
(4) Paso D: ácido 4-(3,4-difluoro-fenoxi)-1H-indol-2-carboxílico (149)

El **152** (380 miligramos, 1.2 milimoles) se disuelve en 10 mililitros de metanol y se trata con una solución de LiOH (57 miligramos, 2.4 milimoles) en 5 mililitros de agua. La mezcla se agita a temperatura ambiente durante 18 horsa. Después de la evaporación, el producto crudo se acidifica a 0°C con HCl 2M y se extrae con acetato de etilo. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan.

Rendimiento: 310 miligramos (90 por ciento) de un sólido amarillo; MS (ESI): 288.1 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 13.0 (s, 1H), 12.0 (s, 1H), 7.45 (m, 1H), 7.25 (d, 1H), 7.18 (dd, 1H), 7.05 (m, 1H), 6.98 (m, 1H), 6.87 (s, 1H), 6.55 (d, 1H).

Ejemplo 123

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amina del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de manera análoga al Ejemplo 1, a

455 456

partir del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico 153 (para la preparación, ver más adelante) y la amina 5.

Rendimiento: 180 miligramos (33.2 por ciento) de un sólido amarillo; MS (ESI): 495.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.21 (d, 1H), 7.33 (d, 1H), 7.2 (dd, 1H), 7.04 (d, 1H), 6.94 (m, 1H), 6.75 (d, 1H), 6.62 (m, 2H), 3.7 (m, 1H), 2.85 (m, 2H), 2.47-2.58 (m, 6H), 2.36 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.47-1.55 (m, 10H).

Síntesis del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico (153):

(1) Paso A: Etil-éster del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico (154)

Se disuelven el etil-éster del ácido 4-hidroxi-1H-indol-2-carboxílico (1 gramos, 4.87 milimoles) y 1,3,5-trifluoro-2-nitro-benceno (0.57 mililitros, 4.87 milimoles) en 10 mililitros de dimetilformamida. Después de la adición de carbonato de potasio (1.3 gramos, 9.74 milimoles), la mezcla se agita durante la noche a temperatura ambiente. Luego la mezcla de reacción se evapora bajo presión reducida, se disuelve con acetato de etilo y se lava con agua. Las capas orgánicas se secan sobre sulfato de sodio y se evapora.

Rendimiento: 1.8 gramos (100 por ciento) de una espuma amarilla; MS (ESI): 361.2 $[M-H]^-$.

(2) Paso B: Etil-éster del ácido 4-(2-amino-3,5-difluoro-fenoxi)-1H-indol-2 carboxílico (155)

El 154 (1.8 gramos, 4.87 milimoles) se disuelve en acetato de

456

etilo y, después de la adición de Pd-C (500 miligramos), la mezcla se hidrogena a temperatura ambiente durante 2 horas. La mezcla se filtra sobre Celite para remover el catalizador y se evapora. Rendimiento: 1.53 gramos (94 por ciento) de una espuma café. MS (ESI): 333.2 $[M+H]^+$.

(3) Paso C: Etil-éster del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico (156)

Se disuelve nitrito de tert-butilo (0.547 mililitros, 4.6 milimoles) en 5 mililitros de dimetilformamida y se calienta a 65°C. Se agrega por goteo una solución del 155 (1.5 gramos, 4.6 milimoles) en dimetilformamida y la mezcla se agita durante 10 minutos adicionales. La solución café se enfría a temperatura ambiente, se diluye con dietil-éter y se lava con HCl 2N y salmuera. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan. El producto crudo (1.5 gramos de un aceite café) se purifica además mediante cromatografía por evaporación (hexano / acetato de etilo 9:1). Rendimiento: 260 miligramos (17.8 por ciento) de un sólido amarillo; MS (ESI): 316.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 12.2 (s, 1H), 7.35 (d, 1H), 7.28 (dd, 1H), 6.95 (m, 1H), 6.82 (d, 1H), 6.79 (d, 1H), 6.68 (dd, 1H), 4.3 (q, 2H), 1.3 (t, 3H).

(4) Paso D: Ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico (153)

El 156 (260 miligramos, 0.82 milimoles) se disuelve en 10 mililitros de metanol y se trata con una solución de LiOH (40 miligramos, 1.6 milimoles) en 5 mililitros de agua. La mezcla se agita

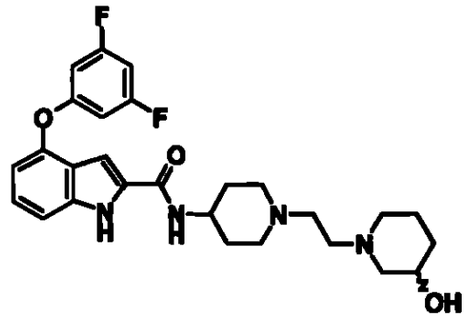
457
#456

a temperatura ambiente durante 18 horas. Después de la evaporación, el producto crudo se acidifica a 0°C con HCl 2M y se extrae con acetato de etilo. Las capas orgánicas se secan sobre sulfato de sodio y se evaporan.

Rendimiento: 2410 miligramos (100 por ciento) de un sólido amarillo;

Ejemplo 124

{1-[2-[3-RS-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico



Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico 153 (ver Ejemplo 123) y la amina racémica 12.

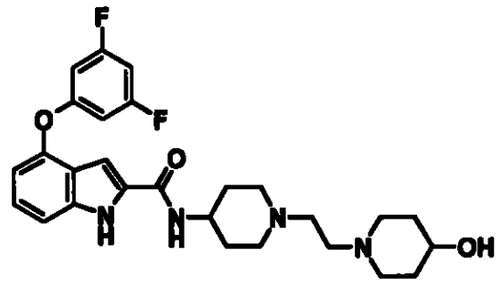
Rendimiento: 38 gramos (32 por ciento) de un sólido blanco; MS (ESI): 499 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.25 (d, 1H), 7.33 (d, 1H), 7.2 (dd, 1H), 7.04 (s, 1H), 6.92 (dd, 1H), 6.76 (d, 1H), 6.63 (d, 2H), 4.02 (d, 1H), 3.72 (m, 1H), 3.4 (m, 1H), 2.8-2.9 (m, 3H), 2.67 (m, 2H), 2.38 (m, 4H), 1.99 (m, 2H), 1.68-1.88 (m, 5H), 1.47-1.6 (m, 3H), 1.371 (m, 1H), 1.05 (m, 1H).

Ejemplo 125

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amina del ácido

458

4-(3,5-difluor -fenoxi)-1H-indol-2-carboxílic

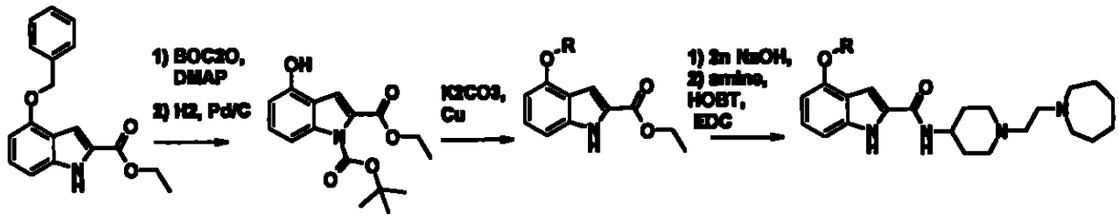


Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir de ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico 153 (ver Ejemplo 123) y la amina 21.

Rendimiento: 23 miligramos (13 por ciento) de un sólido blanco; MS (ESI): 497.2 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.79 (s, 1H), 8.22 (br, 1H), 7.32 (d, 1H), 7.2 (dd, 1H), 7.04 (s, 1H), 6.9 (dd, 1H), 6.75 (d, 1H), 6.6 (d, 2H), 4.46 (s, 1H), 3.72 (m, 1H), 3.39 (m, 1H), 2.83 (m, 2H), 2.67 (m, 2H), 2.35 (m, 4H), 1.98 (m, 4H), 1.75 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.35 (m, 2H).

De manera alternativa, las 4-alcoxi-indol-2-carboxamidas se preparan como se muestra en el esquema de reacción 16

Esquema de Reacción 1116:

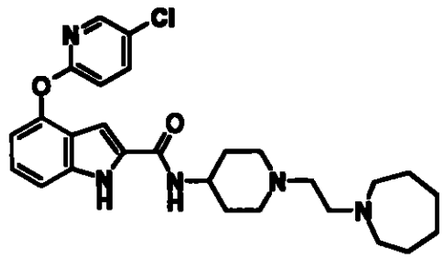


Ejemplo 126

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácid 4-(6-cl ro-

459

piridin2-il xi)-1H-indol-2-carboxílic



Este compuesto se sintetiza de manera análoga al Ejemplo 1, a partir del ácido 4-(6-cloro-piridin-2-iloxi)-1H-indol-2-carboxílico 157 (para la preparación, ver más adelante) y la amina 5.

Rendimiento: 85 miligramos (54 por ciento) de un cristal amarillo; MS (ESI): 494.3 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.2 (d, 1H), 7.85 (dd, 1H), 7.3 (d, 1H), 7.2 (m, 2H), 6.95 (s, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 3.7 (m, 1H), 2.85 (m, 2H), 2.5-2.6 (m, 6H), 2.35 (m, 2H), 2.0 (t, 2H), 1.75 (m, 2H), 1.5 (m, 10H).

Síntesis del ácido 4-(6-cloro-piridin-2-iloxi)-1H-indol-2-carboxílico (157)

(1) 2-etil-éster de 1-terbutil-éster del ácido 4-benciloxi-indol-1,2-dicarboxílico (158)

Se disuelve el etil-éster del ácido 4-benciloxi-1H-indol-2-carboxilico (10 gramos, 34 milimoles) y DMPA (80 miligramos) en 80 mililitros de acetato de etilo. Se agrega BOC20 (8.9 gramos, 41 milimoles) disuelto en una pequeña cantidad de acetato de etilo a temperatura ambiente. La mezcla se agita durante la noche a temperatura ambiente. Luego, la mezcla de reacción se lava con ácido tartárico acuoso 1M, agua y salmuera. Las capas orgánicas se

460
461

secan sobre sulfato de sodio y se evaporan. El producto crudo se utiliza en el siguiente paso sin mayor purificación.

Rendimiento: 13.8 gramos (100 por ciento) de un aceite amarillo; 1H-RMN (CDCl3): δ (ppm) 7.7 (d, 1H), 7.3-7.5 (m, 7H), 6.75 (d, 1H), 5.2 (s, 2H), 4.4 (q, 2H), 1.7 (s, 9H), 1.4 (t, 3H).

(2) Paso B: 2-etil-éster de 1-terbutil-éster del ácido 4-hidroxi-indol-1,2-dicarboxílico (159)

El 158 (8 gramos, 20 milimoles) se disuelve en 80 mililitros de acetato de etilo y, después de la adición del 5 por ciento de Pd-C (700 miligramos), la mezcla se hidrogena a temperatura ambiente durante 7 horas. La mezcla se filtra sobre Celite para remover el catalizador y se evapora. El sólido se suspende en éter / hexano y se filtra.

Rendimiento: 4.6 gramos (74 por ciento). 1H-RMN (CDCl3): δ (ppm) 7.7 (d, 1H), 7.3 (m, 2H), 6.7 (d, 1H), 5.5 (s, 1H), 4.4 (q, 2H), 1.7 (s, 9H), 1.4 (t, 3H).

(3) Paso C: Etil-éster del ácido 4-(6-cloro-piridin-2-iloxi)-1H-indol-2-carboxílico (160)

Se disuelven el 159 (500 miligramos, 1.6 milimoles), 2,6.dicloro-piridin (360 miligramos, 24 milimoles) en 15 mililitros de dimetilformamida. Después de la adición de carbonato de potasio (340 miligramos, 24 milimoles) y una cantidad catalítica de polvo de Cu, la mezcla se calienta a 160°C durante 3 horas. La mezcla de reacción se enfría a temperatura ambiente, se diluye con acetato de etilo y se lava con agua. Las capas orgánicas se secan sobre sulfato

461
#62

de sodio y se evaporan. El producto crudo se resuelve en diclorometano y, después de la evaporación se cristaliza con ciclohexano.

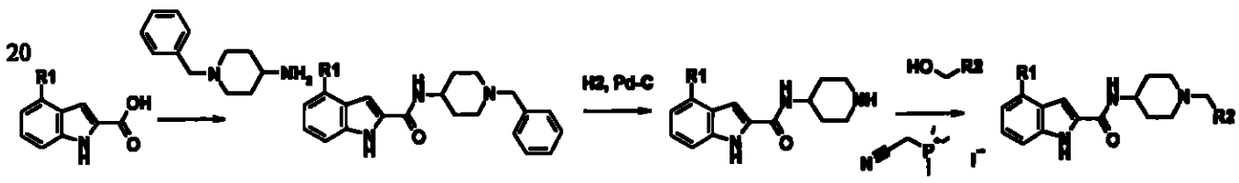
Rendimiento: 300 miligramos (58 por ciento) de un sólido beige; MS (ESI): 317.2 $[M+H]^+$, 1H-RMN (CDCl3): δ (ppm) 9.2 (br, 1H), 7.7 (dd, 1H), 7.3 (m, 2H), 7.1 (m, 2H), 6.95 (dd, 1H), 6.75 (d, 1H), 4.4 (q, 2H), 1.4 (t, 3H).

(4) Paso D: Ácido 4-(6-cloro-piridin-2-iloxi)-1H-indol-2-carboxílico (157)

El 160 (100 miligramos, 0.315 milimoles) se disuelve en 4 mililitros de metanol, y se trata con una solución de NaOH (1 mililitro, 2N). La mezcla se agita 1 hora a temperatura ambiente. La mezcla de reacción se acidifica con HCl (1 mililitro, 2N) y se evapora. La mezcla cruda se utiliza en el siguiente paso sin mayor purificación.

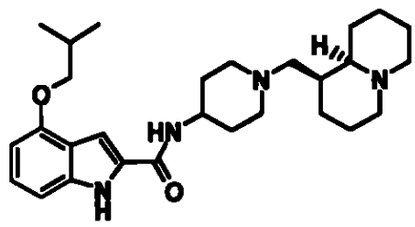
<u>De manera alternativa, las 4-alcoxi-indol-2-carboxamidas se preparan como se muestra en el esquema de reacción 17.</u>

<u>Esquema de Reacción 17:</u>



<u>Ejemplo 127</u>

Diclorhidrato de [1-(octahidro-quinolizin-1-ilmetil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-ind l-2-carboxílic



Se disuelven el 161 (para la preparación, ver más adelante) (2.5 gramos, 7.1 milimoles), octahidro-2H-quinolizin-1-ilmetanol (Lupinina) (1.2 gramos, 7.1 milimoles) y etildi-isopropilamina (12.2 mililitros, 71 milimoles en 10 mililitros de propionitrilo. Después de la adición de yoduro de cianometil-trimetil-fosfonio (4.1 gramos, 17 milimoles) la mezcla se pone a reflujo durante 3 horas. Después de enfriar a temperatura ambiente, la mezcla se diluye con acetato de etilo y se lava con una solución de carbonato de potasio. El producto crudo (3.9 gramos de un aceite café) se cristaliza a partir de metnol. Rendimiento: 2 gramos (52 por ciento) de un sólido blanco; MS (ESI): 467 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.42 (s, NH), 8.16 (d, NH), 7.22 (d, 1H), 7.02 (dd, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 3.83 (d, 2H), 3.75 (m, 1H), 3.49 (s, 2H), 2.81 (m, 2H), 2.70 (m, 2H), 2.29 (m, 1H), 2.15-2.00 (m, 2H), 1.95-1.73 (m, 7H), 1.72-1.27 (m, 9H), 1.26-1.10 (m, 2H), 1.05 (d, 6H).

Síntesis de (1-bencil-piperidin-4-il)-amina del ácido 4-isobutoxi-1H-indol-2-carboxílico

(1) Paso A: (1-bencil-piperidin-4-il)-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico (161)

Se disuelven el ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (4.7

463

gramos, 20.1 milimoles, para la preparación, ver el Ejemplo 8) y 1-bencil-piperidin-4-ilamina (4.2 mililitros, 20.1 milimoles) en N,N-dimetil-formamida y después de la adición de TBTU (7.3 gramos, 22.1 milimoles) y etildi-isopropilamina (13.8 milimoles, 80.4 milimoles), la mezcla se agita a temperatura ambiente durante 2 horas. Luego, el solvente se evapora al alto vacío. El residuo se disuelve en acetato de etilo, se lava con carbonato ácido de sodio acuoso satura y salmuera. Las capas orgánicas se secan sobre sulfato de sodio y se evapora bajo presión reducida.

Rendimiento: 8.96 gramos de un sólido beige; MS (ESI): 406.5 $[M+H]^+$.

(2) Paso B: Clorhidrato de piperidin-4-ilamida del ácido 4-isobutoxi-1H-indol-2-carboxílico (161)

El 161 (8.1 gramos, 20 milimoles) se disuelven en 200 mililitros de etanol y, después de la adición de Pd-C (200 miligramos) y 10 mililitros de HCl 4M, la mezcla se hidrogena a temperatura ambiente durante 3 horas. La mezcla se filtra sobre Celite para remover el catalizador y se evapora.

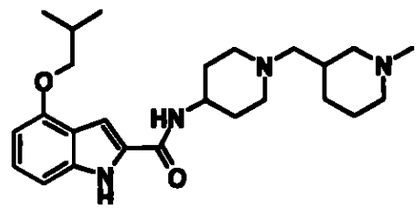
Rendimiento: 7.13 gramos (100 por ciento) de un sólido blanco; MS (ESI): 316 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.42 (d, 1H), 7.25 (s, 2H), 7.04 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 4.0 (m, 1H), 3.83 (d, 2H), 3.22 (m, 2H), 2.88 (m, 2H), 2.1 (m, 1H), 1.9 (m, 2H), 1.7 (m, 2H), 1.05 (d, 6H).

Ejemplo 128

[1-(1-metil-piperidin-3-ilmetil)-piperidin-4-il]-amida del ácido 4-

464

isobutoxi-1H-ind l-2-carboxílico

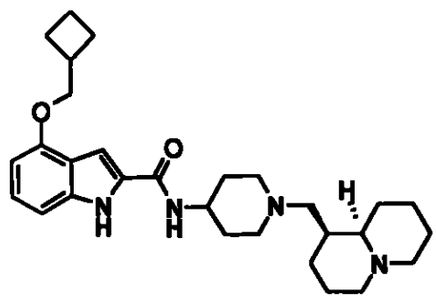


Este compuesto se sintetiza a partir del compuesto 161 (ver Ejemplo 127) y (1-metil-piperidin-3-il)-metanol de manera análoga al método que se describe en el Ejemplo 127.

Rendimiento: 60 miligramos (50 por ciento); MS (ESI): 427 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, NH), 8.18 (d, NH), 7.21 (s, 1H), 7.02 (dd, 1H), 6.95 (d, 1H), 6.45 (d, 1H), 3.85 (d, 2H), 3.75 (m, 1H), 2.88 (m, 1H), 2.78 (m, 2H), 2.62 (m, 1H), 2.12 (s, 3H), 2.13-2.05 (m, 3H), 2.00-1.84 (m, 2H), 1.84-1.40 (m, 10H), 1.05 (d, 6H), 0.82 (m, 1H).

Ejemplo 129

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-clorobutilmetoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir de piperidin-4-ilamida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico, el 162 (para la preparación, ver más adelante) y(1R, 9aR)-1-(octahidro-quinozin-1-

il)-metanol de manera análoga al método descrito en el Ejemplo 127. MS (ESI): 479.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.2 (d, 1H), 7.2 (d, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.04 (d, 2H), 3.76 (m, 1H), 2.6-2.9 (m, 5H), 2.22-2.54 (m, 2H), 1.08-2.17 (m, 26H).

Síntesis de piperidin-4-ilamida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico, 162

(1) Paso A: Tert-butil-éster del ácido 4-[(4-ciclobutilmetoxi-1H-indol-2-carbonil)-amino]-piperidin-1-carboxílico

Se agrega tert-butil-éster del ácido 4-amino-piperidin-1-carboxílico (1.98 gramos, 9.87 milimoles), HOBT (1.37 gramos, 8.97 milimoles), trietilamina (2.5 mililitros, 17.94 milimoles) y EDC (1.72 gramos, 8.97 milimoles) a una solución del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico (82) a partir del Ejemplo 34 (2.2 gramos, 8.97 milimoles) en 20 mililitros de DCM. La mezcla se agita a temperatura ambiente durante la noche. Luego, se lava con NaOH 2N y salmuera, se seca sobre sulfato de sodio anhídrido y se evapora para dar un polvo amarillo. El material crudo se purifica mediante cromatografía sobre gel de sílice utilizando hexano y EtOAc (desde 0 por ciento hasta 20 por ciento).

Rendimiento: 3.02 gramos (79 por ciento); MS (ESI): 426.3 $[M-H]^-$, 1H-RMN ($CDCl_3$): δ (ppm) 9.33 (s, 1H), 7.17 (t, 1H), 7.03 (d, 1H), 6.97 (s, 1H), 6.5 (d, 1H), 6.12 (d, 1H), 4.13 (m, 4H), 4.07 (d, 2H), 2.78-2.97 (m, 4H), 1.88-2.25 (m, 8H), 1.46 (s, 9H).

(2) Paso B: Piperidin-4-ilamida del ácid 4-cicl butilmetoxi-

466

1H-Ind l-2-carboxílico, 162

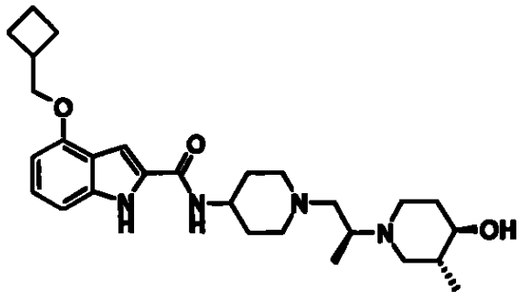
El tert-butil-éster (163) anterior (3.02 gramos, 7.05 milimoles) se disuelve en 20 mililitros de dioxano. Se agrega una solución 4M de HCl en dioxano (14.1 mililitros, 56.4 milimoles) y la mezcla se agita durante 24 horas. La evaporación dio el clorhidrato como un polvo blanco.

Rendimiento: 2.93 gramos (>100 por ciento, no completamente seco).

MS (ESI): 427 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.59 (s, 1H), 8.75 (br m, 2H), 8.51 (d, 1H), 7.25 (s, 1H), 7.07 (t, 1H), 6.99 (d, 1H), 6.5 (d, 1H), 4.1 (m, 1H), 4.05 (d, 2H), 3.25-3.45 (m, 2H), 3.02 (m, 2H), 2.78 (m, 1H), 2.14 (m, 2H), 1.85-2.04 (m, 5H), 1.76 (m, 2H).

Ejemplo 130

{1-[(S)-2-((3R,4R)-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico



Este compuesto se sintetiza a partir de piperidin-4-il-amida del ácido 4-ciclobutil-metoxi-1H-indol-2-carboxílico 162 (ver el Ejemplo 129) y (3R,4R)-1-((R)-2-hidroxi-propil)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico 164 (para la preparación, ver más adelante), de una manera análoga al método descrito en el Ejemplo

127, seguido por disociación de pivaloílo, como se describe para la amina 55.

MS (ESI): 483.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (br s, 1H), 7.19 (s, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.44 (m, 1H), 4.04 (d, 2H), 3.73 (m, 1H), 2.58 - 2.96 (m, 7H), 2.04 - 2.41 (m, 6H), 1.83 - 2.02 (m, 6H), 1.66 - 1.82 (m, 3H), 1.45 - 1.65 (m, 2H), 1.2 - 1.44 (m, 2H), 0.91 (d, 3H), 0.86 (d, 3H).

(1) (3R,4R)-1-((R)-2-hidroxi-propil)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (164).

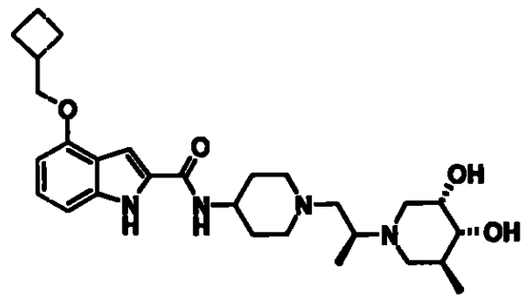
Una solución de piperidina 20 (3 gramos, 15.05 milimoles) y (R)-2-metil-oxirano (15.05 mililitros, 150.5 milimoles) en 10 mililitros de etanol, se agita durante 24 horas en un matraz cerrado. El solvente se evapora y el residuo se destila en un aparato Kugelrohr (0.08 mbar, 80-90°C).

Rendimiento: 3.82 gramos (99 por ciento). MS (ESI): 258.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 4.34 (br s, 1H), 4.24 (td, 1H), 3.70 (sexteto, 1H), 2.79 (m, 2H), 2.03 - 2.28 (m, 3H), 1.65 - 1.9 (m, 3H), 1.45 (qd, 1H), 1.14 (s, 9H), 1.02 (d, 3H), 0.81 (d, 3H), $[\alpha]_D$ = -66.1 (c = 1.5 en MeOH).

Ejemplo 131

{1-[(S)-2-((3S,4R,5S)-3,4-dihidroxi-5-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutil-metoxi-1H-indol-2-carboxílico.

468
469

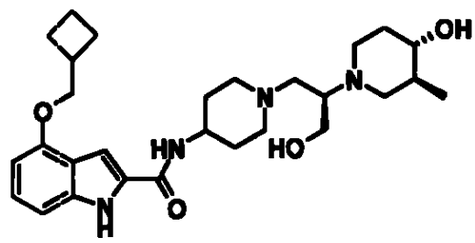


Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-ciclobutil-metoxi-1H-indol-2-carboxílico 162 (ver el Ejemplo 129) y la amina 35, de una manera análoga al método descrito en 54, seguido por disociación del grupo protector.

MS (ESI): 499.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.47 (s, 1H), 8.28 (br s, 1H), 7.23 (s, 1H), 7.04 (t, 1H), 6.99 (d, 1H), 6.49 (d, 1H), 4.07 (m, 1H), 4.06 (d, 2H), 4.02 (m, 1H), 3.76 (m, 1H), 3.55 (m, 1H), 2.58 - 2.96 (m, 6H), 2.25 - 2.4 (m, 3H), 1.83 - 2.15 (m, 11H), 1.66 - 1.82 (m, 2H), 1.45 - 1.65 (m, 2H), 0.91 (d, 3H), 0.86 (d, 3H).

Ejemplo 132

{1-[(R)-3-hidroxi-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclo-butil-metoxi-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-ciclo-butil-metoxi-1H-indol-2-carboxílico 162 (ver el

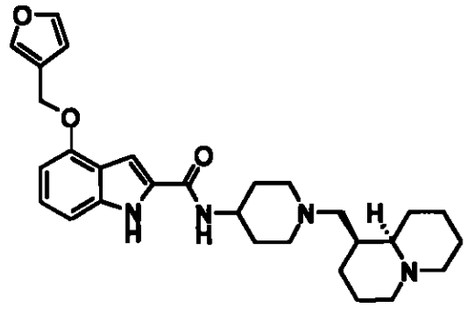
469

Ejemplo 129) y el (3S,4S)-1-((S)-2-hidroxi-3-tritiloxi-propil)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (60), de una manera análoga al método descrito en 56, seguido por la remoción subsecuente de los grupos de protección con metilato de sodio y ácido acético al 80 por ciento.

MS (ESI): 499.5 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.44 (s, 1H), 8.22 (d, 1H), 7.2 (d, 1H), 7.03 (t, 1H), 6.96 (d, 1H), 6.47 (d, 1H), 4.45 (d, 1H), 4.28 - 4.45 (m, 1H), 4.04 (d, 2H), 3.7 - 3.8 (m, 1H), 3.42 (d, 2H), 2.6 - 2.98 (m, 7H), 1.15 - 2.18 (m, 16H), 0.86 (d, 3H).

Ejemplo 133

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico 165 (para la preparación, ver más adelante), y (1R,9aR)-1-(octahidro-quinolizin-1-il)-metanol, de una manera análoga al método descrito en el Ejemplo 127.

MS (ESI): 491.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.13 (d, 1H), 7.82 (s, 1H), 7.68 (t, 1H), 7.22 (d, 1H), 7.05 (t, 1H),

6.98 (d, 1H), 6.62 (s, 1H), 6.59 (d, 1H), 5.03 (s, 2H), 3.74 (m, 1H), 2.8 (m, 2H), 2.69 (m, 2H), 2.43 - 2.53 (m, 1H), 2.27 (m, 1H), 2.02 (m, 1H), 1.07 - 1.95 (m, 19H).

Síntesis de piperidin-4-il-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico (165)

(1) Paso A: Terbutil-éster del ácido 4-{[4-(furan-3-il-metoxi)-1H-indol-2-carbonil]-amino}-piperidin-1-carboxílico (166).

A una solución del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico (95) del Ejemplo 33 (5 gramos, 19.44 milimoles) en 10 mililitros de DCM, se le agrega terbutil-éster del ácido 4-amino-piperidin-1-carboxílico (3.89 gramos, 19.44 milimoles), HOBT (2.98 gramos, 19.44 milimoles), trietil-amina (5.4 mililitros, 38.88 milimoles), y EDC (3.73 gramos, 19.44 milimoles). La mezcla se agita a temperatura ambiente durante la noche. Luego se lava con NaOH 2N y salmuera, se seca sobre sulfato de sodio anhidro, y se evapora para dar un polvo amarillo. El material crudo se purifica mediante cromatografía sobre gel de sílice utilizando DCM y EtOAc (desde el 0 por ciento hasta el 10 por ciento).

Rendimiento: 7.51 gramos (88 por ciento). MS (ESI): 438.3 $[M-H]^-$, 1H-RMN ($CDCl_3$): δ (ppm) 9.42 (s, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.21 (t, 1H), 7.05 (d, 1H), 6.96 (s, 1H), 6.6 (d, 1H), 6.55 (s, 1H), 6.08 (d, 1H), 5.07 (d, 2H), 4.04 - 4.2 (m traslapado, 3H), 2.91 (m, 2H), 2.01 (m, 2H), 1.48 (s, 9H), 1.42 (m, 2H).

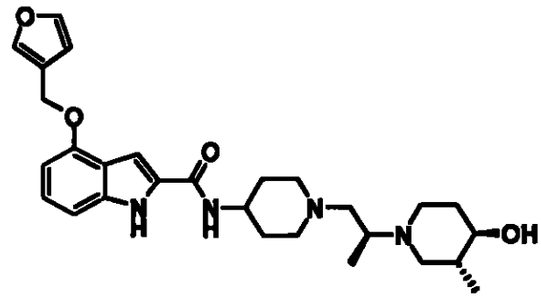
(2) Paso B: Piperidin-4-il-amida del ácido 4-(furan-3-il-met xl)-1H-indol-2-carboxílico (165).

El terbutil-éster (166) anterior (695 miligramos, 1.58 milimoles) se disuelve en 5 mililitros de dioxano. Se agrega una solución 4M de HCl en dioxano (3.2 mililitros, 12.8 milimoles), y la mezcla se agita durante 24 horas. La evaporación dio el clorhidrato como un polvo blanco.

Rendimiento: 595 miligramos (100 por ciento). MS (ESI): 340.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 9.0 (br m, 2H), 8.5 (d, 1H), 7.85 (s, 1H), 7.71 (s, 1H), 7.3 (s, 1H), 7.09 (t, 1H), 7.02 (d, 1H), 6.62 (d, 1H), 6.64 (s, 1H), 5.05 (d, 2H), 4.07 (m, 1H), 3.31 (m, 2H), 3.0 (m, 2H), 1.96 (m, 2H), 1.78 (m, 2H).

Ejemplo 134

{1-[(S)-2-((3R,4R)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico 165 (ver el Ejemplo 133), y el (3R,4R)-1-((R)-2-hidroxi-propil)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico 164 (para la preparación, ver el Ejemplo 130), de una manera análoga al método descrito en el Ejemplo 127, seguido por disociación de pivaloílo como se describe

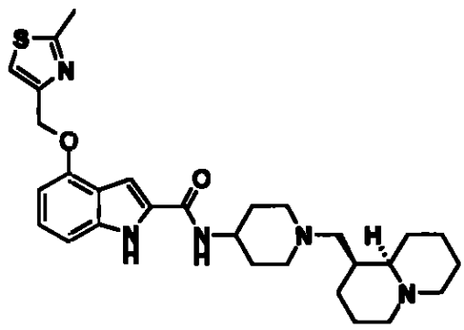
471

para la amina 55.

MS (ESI): 495.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (br s, 1H), 7.23 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.6 (d, 1H), 5.03 (s, 2H), 4.43 (d, 1H), 3.72 (m, 1H), 2.56 - 2.95 (m, 5H), 2.32 (m, 1H), 2.24 (m, 1H), 2.04 - 2.19 (m, 2H), 1.9 (m, 2H), 1.67 - 1.79 (m, 3H), 1.43 - 1.61 (m, 2H), 1.21 - 1.41 (m, 3H), 0.91 (d, 3H), 0.86 (d, 3H).

Ejemplo 135

[1-(octahidro-quinolizin-1-il-metil)-piperidin-4-il]-amida del ácido 4-(2-metil-tiazol-4-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-(2-metil-tiazol-4-il-metoxi)-1H-indol-2-carboxílico 167 (para la preparación, ver más adelante), y (1R,9aR)-1-(octahidro-quinolizin-1-il)-metanol, de una manera análoga al método descrito en el Ejemplo 127.

MS (ESI): 522 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.15 (d, 1H), 7.57 (s, 1H), 7.25 (s, 1H), 7.05 (dd, 1H), 6.98 (d, 1H), 6.62 (s, 1H), 5.18 (s, 2H), 3.74 (m, 1H), 2.8 (m, 2H), 2.69 (m, 2H),

2.68 (s, 3H), 2.43 - 2.53 (m, 1H), 2.27 (m, 1H),j 2.02 (m, 1H), 1.07 - 1.95 (m, 19H).

Síntesis de piperidin-4-il-amida del ácido 4-(2-metil-tiazol-4-il-metoxi)-1H-indol-2-carboxílico (167)

(1) Paso A: (2-metil-tiazol-4-il)-metanol (168).

Se disuelve el etil-éster del ácido 2-metil-tiazol-4-carboxílico (966 miligramos, 5.64 milimoles) en 5 mililitros de dietil-éter, y se enfría a -78°C. Se agrega por goteo una solución 1M de hidruro de litio y aluminio en tetrahidrofurano (16.9 mililitros, 16.9 milimoles), y la mezcla se agita durante 3.5 horas a -78°C. La mezcla se apaga a esta temperatura con una solución saturada de sulfato de sodio, y se deja calentar a temperatura ambiente, seguido por extracción con éter y evaporación.

Rendimiento: 670 miligramos (92 por ciento). MS (ESI): 130.0 $[M-H]^-$, 1H-RMN ($CDCl_3$): δ (ppm) 7.20 (s, 1H), 5.27 (dd, 1H), 4.50 (d, 2H), 2.62 (s, 3H).

(2) Paso B: 2-etil-éster de 1-terbutil-éster del ácido 4-(2-metil-tiazol-4-il-metoxi)-indol-1,2-dicarboxílico (169).

Se disuelve el (2-metil-tiazol-4-il)-metanol 168 (670 miligramos, 5.2 milimoles) en 12 mililitros de tetrahidrofurano seco bajo argón, seguido por la adición del 2-etil-éster de 1-terbutil-éster del ácido 4-hidroxi-indol-1,2-dicarboxílico 102 (ver el Ejemplo 42, 1.58 gramos, 5.2 milimoles), trifenil-fosfina (1.63 gramos, 6.2 milimoles), y la solución se enfría a 0°C. Se agrega por goteo una solución al 40 por ciento de aza-dicarboxilato de etilo en tolueno (2.7 mililitros, 6.2

milimoles), y la mezcla se agita durante 2.5 horas a 0°C. Los solventes se remueven bajo presión reducida, y el residuo se disuelve en acetato de etilo, y se lava con una solución de carbonato ácido de sodio, y salmuera. Las capas orgánicas se secan sobre sulfato de sodio, se filtran, y se evaporan. El producto crudo se purifica mediante cromatografía por evaporación (gel de sílice, acetato de etilo / hexanos, 3:7).

Rendimiento: 1.75 gramos (81 por ciento). MS (ESI): 417.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.67 (s, 1H), 7.55 (d, 1H), 7.41 (dd, 1H), 7.27 (s, 1H), 6.99 (d, 1H), 5.27 (s, 2H), 4.31 (q, 2H), 2.68 (s, 3H), 1.57 (s, 9H), 1.32 (t, 3H).

(3) Paso C: Ácido 4-(2-metil-tiazol-4-il-metoxi)-1H-indol-2-carboxílico (170).

Se disuelve el 2-etil-éster de 1-terbutil-éster del ácido 4-(2-metil-tiazol-4-il-metoxi)-indol-1,2-dicarboxílico (169) (1.75 gramos, 4.2 milimoles) en 20 mililitros de etanol. Después de la adición de una solución acuosa de hidróxido de sodio 0.5 M (33.6 mililitros, 16.8 milimoles), la solución se calienta a 60°C, y se agita a esta temperatura durante 18 horas. Luego se evapora la mezcla de reacción, y el residuo se disuelve en acetato de etilo. A 0°C, se agrega HCl concentrado, hasta que se alcance un pH de 1. La fase orgánica se lava con agua y salmuera. Las capas orgánicas se secan sobre sulfato de sodio, y se filtran. El producto se cristalizó después de la evaporación, y se pudo filtrar.

Rendimiento: 1.21 gramos (100 por ciento). MS (ESI): 289.0 $[M+H]^+$,

1H-RMN (DMSO-d_6): δ (ppm) 11.76 (br s, 11H), 7.62 (s, 1H), 7.14 (dd, 1H), 7.07 (s, 1H), 7.02 (d, 1H), 6.66 (d, 1H), 5.22 (s, 2H), 2.68 (s, 3H).

(4) Paso D: Terbutil-éster del ácido 4-{[4-(2-metil-tiazol-4-il-metoxi)-1H-indol-2-carbonil]-amino}-piperidin-1-carboxílico (171).

Se disuelve el ácido 4-(2-metil-tiazol-4-il-metoxi)-1H-indol-2-carboxílico (170) (1.21 gramos, 4.2 milimoles) en 10 mililitros de N,N-dimetil-formamida, y la solución se enfría a 0°C. Después de la adición de base de Hunig (2.16 mililitros, 12.6 milimoles), terbutil-éster del ácido piperidin-4-il-carbámico (3) (841 miligramos, 4.2 milimoles), y PyBOP (2.4 gramos, 4.6 milimoles), la mezcla se agita a temperatura ambiente durante 18 horas. Se agrega acetato de etilo, seguido por hidróxido de sodio concentrado, hasta que se alcanza un pH de 11. La capa orgánica se lava con salmuera, se seca sobre sulfato de sodio, y se evapora bajo presión reducida. El producto crudo se purifica mediante cromatografía por evaporación (gel de sílice, acetato de etilo / ciclohexano, 1:1).

Rendimiento: 1.58 gramos (80 por ciento). MS (ESI): 471.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.58 (br s, 1H), 8.25 (d, 1H), 7.61 (s, 1H), 7.27 (s, 1H), 7.09 (dd, 1H), 7.02 (d, 1H), 6.63 (d, 1H), 5.18 (s, 2H), 3.93 (m, 3H), 2.85 (m, 2H), 2.69 (s, 3H), 1.78 (m, 2H), 1.4 (s, 9H), 1.38 (m, 2H).

(5) Paso E: Piperidin-4-il-amida del ácido 4-(2-metil-tiazol-4-il-metoxi)-1H-indol-2-carboxílico (167).

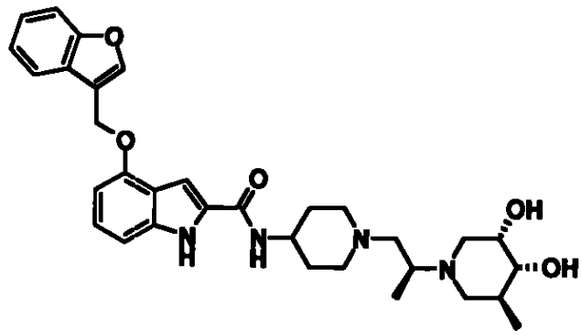
El 171 anterior (1.58 gramos, 3.36 milimoles) se disuelve en

una solución 4M de HCl en dioxano (32 mililitros, 128 milimoles), y se agita durante 45 minutos a temperatura ambiente. Luego la mezcla de reacción se evapora, se disuelve en acetato de etilo, y se agrega hidróxido de sodio concentrado, hasta que se alcanza un pH de 11. La capa acuosa se lava con salmuera, se seca sobre sulfato de sodio, y se evapora bajo presión reducida.

Rendimiento: 1.28 gramos (100 por ciento). MS (ESI): 371.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.56 (br, 1H), 8.28 (d, 1H), 7.61 (s, 1H), 7.3 (s, 1H), 7.09 (dd, 1H), 7.02 (d, 1H), 6.62 (d, 1H), 5.19 (s, 2H), 3.90 (m, 1H), 3.07 (m, 2H), 2.70 (s, 3H), 2.62 - 2.75 (m, 2H), 1.72 - 1.85 (m, 3H), 1.4 - 1.55 (m, 2H).

Ejemplo 136

{1-[2-(3,4-dihidroxi-5-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-(benzofuran-3-il-metoxi)-1H-indol-2-carboxílico 172 (para la preparación, ver más adelante), y la amina 35, de una manera análoga al método descrito en 54, seguido por la disociación del grupo protector.

MS (ESI): 561 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.48 (s, 1H), 8.16 (s, 1H), 8.15 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7;35 (dd, 1H), 7.29 (dd, 1H), 7.19 (s, 1H), 7.09 (dd, 1H), 7.01 (d, 1H), 6.71 (d, 1H), 5.35 (s, 2H), 4.04 (d, 1H), 3.98 (m, 1H), 3.72 (m, 1H), 3.53 (m, 1H), 2.50 - 2.90 (m, 7H), 2.24 -2.38 (m, 2H), 1.88 - 2.08 (m, 3H), 1.66 - 1.78 (m, 3H), 1.45 -1.58 (m, 2H), 0.86 (d, 3H), 0.83 (d, 3H).

Síntesis de piperidin-4-il-amida del ácido 4-(benzofuran-3-il-metoxi)-1H-indol-2-carboxílico (172)

(1) Paso A: Terbutil-éster del ácido 4-{[4-(benzo-furan-3-il-metoxi)-1H-indol-2-carbonil]-amino}-piperidin-1-carboxílico (173).

A una solución helada del ácido 4-(benzofuran-3-il-metoxi)-1H-indol-2-carboxílico 105 (ver el Ejemplo 50) (200 miligramos, 0.651 milimoles) en 2 mililitros de dimetil-formamida, se le agrega base de Hunig (334 microlitros, 1.95 milimoles). Después de agitar a 0°C durante 10 minutos, se agregan subsecuentemente terbutil-éster del ácido 4-amino-piperidin-1-carboxílico (130 miligramos, 0.651 milimoles) y PyBOP (356 miligramos, 0.684 milimoles). La mezcla se agita a temperatura ambiente durante la noche. Luego se diluye con acetato de etilo, se lava con NaOH 1N y salmuera, se seca sobre sulfato de sodio anhidro, y se evapora para dar 980 miligramos de un aceite castaño claro. El material crudo se purifica mediante cromatografía sobre gel de sílice utilizando ciclohexano y acetato de etilo (1:1).

Rendimiento: 318 miligramos (100 por ciento). MS (ESI): 488.2 $[M-H]^-$, 1H-RMN ($CDCl_3$): δ (ppm) 9.15 (s, 1H), 7.77 (s, 1H), 7.72 (d, 1H),

7.55 (d, 1H), 7.38 (dd, 1H), 7.3 (dd, 1H), 7.23 (d, 1H), 7.08 (d, 1H), 6.91 (s, 1H), 6.7 (d, 1H), 5.96 (d, 1H), 5.34 (s, 2H), 4.04 - 4.2 (m traslapado, 3H), 2.91 (m. 2H), 2.01 (m, 2H), 1.48 (s, 9H), 1.40 (m, 2H).

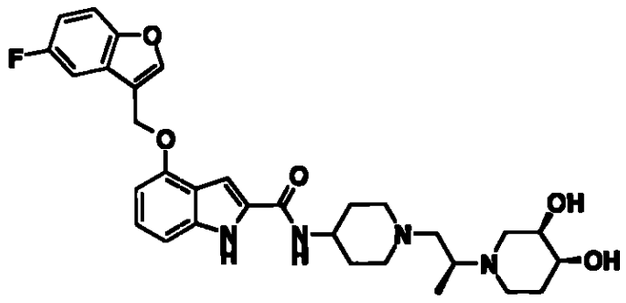
(2) Paso B: Piperidin-4-il-amida del ácido 4-(benzo-furan-3-il-metoxi)-1H-indol-2-carboxílico (172).

El terbutil-éster (173) anterior (318 miligramos, 0.65 milimoles) se disuelve en una solución 4M de HCl en dioxano (6 mililitros, 1.2 milimoles), y se agita durante 1 hora a temperatura ambiente. La evaporación dio el clorhidrato como un polvo blanco, el cual se disuelve en agua, se trata con una solución concentrada de NaOH a 0°C hasta un pH de 11, y se extrae con acetato de etilo. Las capas orgánicas se lavan con salmuera, se secan sobre sulfato de sodio, y se evaporan.

Rendimiento: 248 miligramos (98 por ciento) de un sólido amarillo claro. MS (ESI): 390.2 $[M+H]^+$.

Ejemplo 137

{1-[2-(3,4-dihidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-(5-fluoro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico 174 (para la preparación, ver más adelante), y al amina 34, de una manera análoga al método descrito para el 54, seguido por la disociación del grupo protector.

MS (ESI): 565 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.52 (s, 1H), 8.28 (s, 1H), 7.68 (dd, 1H), 7.52 (d, 1H), 7.23 (s, 1H), 7.21 (dd, 1H), 7.11 (dd, 1H), 7.03 (d, 1H), 6.72 (d, 1H), 5.35 (s, 2H), 4.19 (m, 1H), 4.13 (d, 1H), 3.73 (m, 1H), 3.52 (br s, 1H), 3.44 (br s, 1H), 2.9 (m, 3H), 2.52 (m, 2H), 2.33 (m, 3H), 2.11 (m, 1H), 2.03 (dd, 1H), 1.84 (dd, 1H), 1.75 (d, 1H), 1.45 - 1.65 (m, 5H), 0.9 (d, 3H).

Síntesis de piperidin-4-il-amida del ácido 4-(5-fluoro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico (174)

(1) Paso A: Terbutil-éster del ácido 4{[4-(5-fluoro-benzofuran-3-il-metoxi)-1H-indol-2-carbonil]-amino}-piperidin-1-carboxílico (175).

Una solución del ácido 4-(5-fluoro-benzo-furan-3-il-metoxi)-1H-indol-2-carboxílico 113 (ver el Ejemplo 60, 160 miligramos, 0.49 milimoles), se disuelve en 1.5 mililitros de N,N-dimetil-formamida, y se enfría a 0°C. Después de la adición de base de Hunig (252 microlitros, 1.5 milimoles), la mezcla se agita durante 15 minutos, y luego se agrega terbutil-éster del ácido piperidin-4-il-carbámico 3 (98.5 miligramos, 0.49 milimoles), seguido por PyBOP (269 miligramos, 0.51 milimoles). La mezcla se agita a temperatura ambiente durante 18 horas. Luego la mezcla se diluye con acetato de

etilo, se lava con una solución de hidróxido de sodio 1N, y salmuera. Las capas orgánicas se secan sobre sulfato de sodio, y se evaporan bajo presión reducida. El producto crudo (581 miligramos) se purifica mediante cromatografía por evaporación (gel de sílice, ciclohexano / acetato de etilo, 1:1).

Rendimiento: 250 miligramos (100 por ciento). MS (ESI): 506.2 $[M-H]^-$

(2) Paso B: Piperidin-4-il-amida del ácido 4-(5-fluoro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico (174).

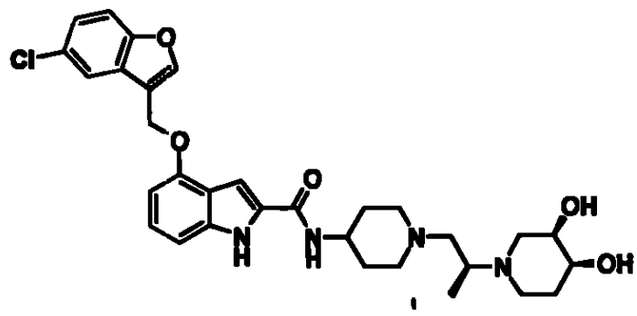
El terbutil-éster (175) anterior (250 miligramos, 0.49 milimoles) se disuelve en una solución 4M de HCl en dioxano (4 mililitros, 16 milimoles), y la mezcla se agita durante 1 hora a temperatura ambiente. La evaporación dio el clorhidrato como un sólido amarillo, el cual se disuelve en 5 mililitros de agua, y el pH se ajusta a 11 mediante la adición de hidróxido de sodio concentrado. La solución se extrae con acetato de etilo, las capas orgánicas se lavan con salmuera y se secan sobre sulfato de sodio. La evaporación dio 200 miligramos (100 por ciento) de un sólido blanco.

MS (ESI): 408.2 $[M+H]^+$.

Ejemplo 138

{1-[2-(3,4-dihidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico.

480



Este compuesto se sintetiza a partir de la piperidin-4-il-amida del ácido 4-(5-cloro-benzo-furan-3-il-metoxi)-1H-indol-2-carboxílico 176 (para la preparación, ver más adelante), y la amina 34, de una manera análoga al método descrito para el 54, seguido por la disociación del grupo protector.

MS (ESI): 581 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (br s, 1H), 8.28 (s, 1H), 8.17 (d, 1H), 7.79 (s, 1H), 7.68 (d, 1H), 7.39 (d, 1H), 7.22 (s, 1H), 7.10 (dd, 1H), 7.03 (d, 1H), 6.7 (d, 1H), 5.36 (s, 2H), 4.18 (m, 1H), 4.12 (d, 1H), 3.72 (m, 1H), 3.52 (m, 1H), 3.45 (m, 1H), 2.45 - 2.9 (m, 4H), 2.33 (m, 4H), 1.88 - 2.14 (m, 3H), 1.73 (m, 2H), 1.42 - 1.65 (m, 4H), 0.89 (d, 3H).

Síntesis de piperidin-4-il-amida del ácido 4-(5-cloro-benzo-furan-3-il-metoxi)-1H-indol-2-carboxílico (176)

(1) Paso A: Terbutil-éster del ácido 4-{[4-(5-cloro-benzo-furan-3-il-metoxi)-1H-indol-2-carbonil]-amino}-piperidin-1-carboxílico (177).

Este compuesto se sintetiza a partir del ácido 4-(5-cloro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico 113 (ver el Ejemplo 60), y la amina 3, de una manera análoga al método descrito para el

175.

Rendimiento: 270 miligramos (60 por ciento). MS (ESI): 522 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.58 (m, 1H), 8.28 (s, 1H), 8.20 (d, 1H), 7.8 (s, 1H), 7.69 (d, 1H), 7.4 (d, 1H), 7.2 (s, 1H), 7.11 (dd, 1H), 7.03 (d, 1H), 6.72 (d, 1H), 5.36 (s, 2H), 3.93 (m, 3H), 2.7 - 2.9 (m, 2H), 1.76 (d, 2H), 1.4 (s, 9H), 1.29 - 1.42 (m, 2H).

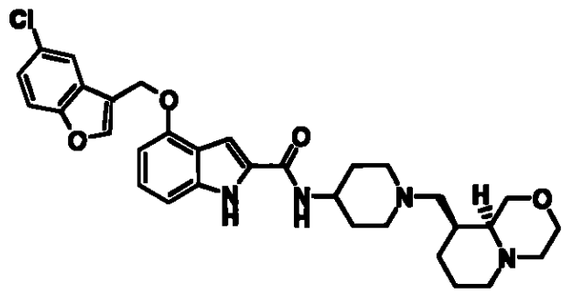
(2) Paso B: Piperidin-4-il-amida del ácido 4-(5-cloro-benzo-furan-3-il-metoxi)-1H-indol-2-carboxílico (176).

Este compuesto se sintetiza a partir del 177 de una manera análoga al método descrito para el 175.

MS (ESI): 424.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.38 (s, 1H), 8.14 (s, 1H), 8.02 (d, 1H), 7.66 (s, 1H), 7.55 (d, 1H), 7.27 (d, 1H), 7.09 (s, 1H), 6.98 (dd, 1H), 6.91 (d, 1H), 6.59 (d, 1H), 5.23 (s, 2H), 3.68 (m, 1H), 2.8 (m, 1H), 2.37 (m, 3H), 1.57 (m, 1H), 1.25 (m, 3H).

Ejemplo 139

{1-[(9S,9aS)-1-(octahidro-pirido[2,1-c][1,4]oxazin-9-il)-metil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzo-furan-3-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 176 (ver el Ejemplo 138), y el (9RS,9aSR)-1-(octahidro-pirido[2,1-c][1,4-oxazin-

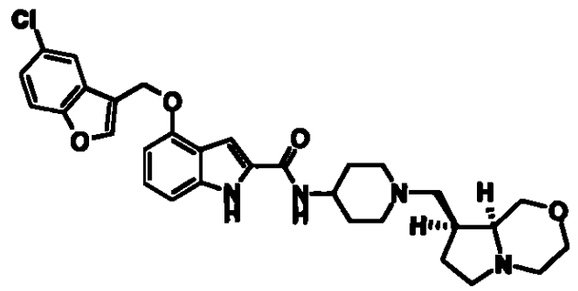
482

9-il)-metanol (63), de una manera análoga al método descrito en el Ejemplo 127.

Rendimiento: 7.7 miligramos (12 por ciento) de un sólido blanco. MS (ESI): 575/577 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.11 (d, 1H), 7.78 (d, 1H), 7.67 (d, 1H), 7.38 (dd, 1H), 7.18 (d, 1H), 7.10 (m, 1H), 7.03 (d, 1H), 6.70 (d, 1H), 5.36 (s, 2H), 3.75 - 3.60 (m, 2H), 3.50 - 3.30 (m, 4H), 2.80 - 2.55 (m, 2H), 2.60 - 2.50 (m, 2H), 2.32 (d, 2H), 2.10 - 1.65 (m, 9H), 1.60 - 1.40 (m, 3H), 1.35 - 1.20 (m, 2H).

Ejemplo 140

{1-[(8S,8aS)-1-(hexahidro-pirrolo[2,1-c][1,4]oxazin-8-il)-metil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzo-furan-3-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 176 (ver el Ejemplo 138) y el (9RS,9aSR)-1-(octahidro-pirido-[2,1-c][1,4]oxazin-9-il)-metanol (67), de una manera análoga al método descrito en el Ejemplo 127.

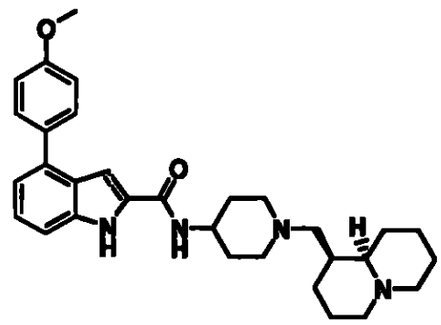
Rendimiento: 82 miligramos (14.6 por ciento) de un sólido blanco. MS (ESI): 563/565 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H),

483

8.25 (s, 1H), 8.10 (d, 1H), 7.78 (d, 1H), 7.67 (d, 1H), 7.38 (bd, 1H), 7.19 (s, 1H), 7.10 - 7.00 (m, 2H), 6.70 (d, 1H), 5.35 (s, 2H), 4.00 (m, 1H), 3.90 (m, 1H), 3.75 -3.60 (m, 2H), 3.40 - 3.30 (m, 2H), 2.95 - 2.70 (m, 1H), 2.40 -2.20 (m, 2H), 2.10 - 1.70 (m, 8H), 1.55 - 1.25 (m, 4H), 1.15 (t, 1H), 1.07 (t, 1H).

Ejemplo 141

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 178 (para la preparación, ver más adelante), y octahidro-2H-quinolizin-1-il-metanol, de una manera análoga al método descrito en el Ejemplo 127.

Rendimiento: 350 miligramos (33.7 por ciento). MS (ESI): 501 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.22 (d, 1H), 7.56 (d, 2H), 7.37 (d, 1H), 7.31 (m, 1H), 7.20 (dd, 1H), 7.07 (d, 2H), 7.01 (d, 1H), 3.81 (s, 3H), 3.75 (m, 1H), 3.16 (d, 1H), 2.80 (m, 2H), 2.67 (m, 2H), 2.46 (dd, 1H), 2.28 (m, 1H), 1.1 - 2.1 (m, 19H).

Síntesis de piperidin-4-il-amida del ácid 4-(4-met xi-fenil)-1H-

484

Indol-2-carboxílico (178):

(1) Paso A: Ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico (128).

Se disuelven ácido 4-bromo-1H-indol-2-carboxílico (5 gramos, 20.8 milimoles), y ácido 4-metoxi-fenil-borónico (3.2 gramos, 20.8 milimoles), en 1-propanol (100 mililitros), y la mezcla se inunda con argón durante 30 minutos. Luego se agregan cloruro de bis(trifenilfosfina)paladio(II) (200 miligramos, 1 milimol), y Na_2CO_3 (4.4 gramos, 40.2 milimoles), y la mezcla de reacción se agita a 85°C durante 3 horas. Después de enfriarse a temperatura ambiente, se agregan acetato de etilo y HCl 2M. Las capas orgánicas se secan sobre sulfato de sodio. La evaporación dio 6 gramos de un sólido beige, el cual se purifica adicionalmente mediante cristalización a partir de acetato de etilo.

Rendimiento:4.7 gramos (84 por ciento).MS (ESI):266 $[M-H]^-$.

(2) Paso B: (1-bencil-piperidin-4-il)-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico (179).

Se disuelven el 128 (4.7 gramos, 17.6 milimoles) y 1-bencil-piperidin-4-il-amina (3.3 gramos, 17.6 milimoles) en N,N-dimetil-formamida (70 mililitros), y después de la adición de TBTU (6.4 gramos, 19.4 milimoles) y etil-di-isopropil-amina (12 mililitros, 70.4 milimoles), la mezcla se agita a temperatura ambiente durante 2 horas. Luego se evapora el solvente a una alto vacío. El residuo se disuelve en acetato de etilo, se lava con carbonato ácido de sodio acuoso saturado, y salmuera. Las capas orgánicas se secan sobre

sulfato de sodio, y se evaporan bajo presión reducida. La mezcla cruda se cristaliza a partir de metanol.

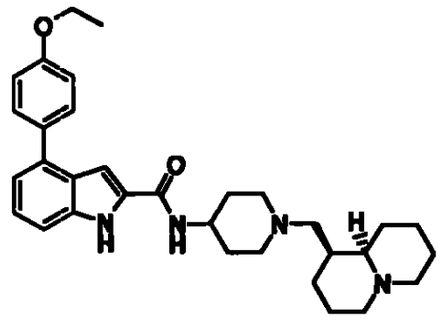
Rendimiento: 4.1 gramos (53 por ciento). MS (ESI): 440 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.26 (d, 1H), 7.56 (d, 2H), 7.38 (d, 1H), 7.15 - 7.35 (m, 7H), 7.08 (d, 2H), 7.01 (d, 1H), 4.07 (m, 1H), 3.81 (s, 3H), 3.47 (s, 2H), 2.8 (m, 2H), 2.04 (m, 2H), 1.77 (m, 2H), 1.58 (m, 2H).

(3) Paso C: Piperidin-4-il-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico (178).

Se disuelve el 179 (4 gramos, 9.1 milimoles) en 100 mililitros de metanol, se inunda con argón, y, después de la adición de Pd-C (100 miligramos) y HCl 2M (5.5 mililitros, 11 milimoles), la mezcla se hidrogena a temperatura ambiente durante 3 horas. La mezcla se filtra sobre Celite, y se evapora. Rendimiento: 1 gramo de un sólido blanco (29 por ciento). MS (ESI): 350 $[M+H]^+$.

Ejemplo 142

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 180 (para la preparación, ver más adelante), y octahidro-2H-quinolizin-1-il-metanol, de una manera análoga al método descrito en el Ejemplo 127.

Rendimiento: 23 miligramos (16.2 por ciento). MS (ESI): 515 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.67 (s, 1H), 8.28 (d, 1H), 7.56 (d, 2H), 7.33 (d, 1H), 7.3 (m, 1H), 7.20 (dd, 1H), 7.0 - 7.07 (m, 3H), 4.08 (q, 2H), 3.77 (m, 1H), 2.80 (dd, 2H), 2.67 (m, 2H), 2.46 (dd, 1H), 2.28 (dd, 1H), 2.01 (dd, 1H), 1.36 (t, 3H), 1.1 - 2.1 (m, 19H).

Síntesis de piperidin-4-il-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico (180):

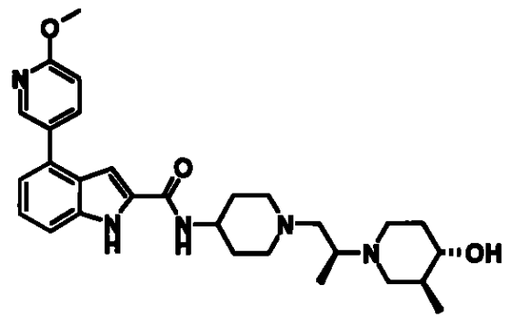
Este compuesto se ha sintetizado a partir del ácido 4-etoxi-fenil-borónico, de una manera análoga al método descrito en la síntesis del 178 (ver el Ejemplo 141).

MS (ESI): 364 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.64 (s, 1H), 8.28 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.31 (s, 1H), 7.19 (dd, 1H), 7.06 (d, 2H), 7.02 (d, 1H), 4.09 (q, 2H), 3.81 (m, 1H), 3.4 (m, 1H), 2.92 (m, 2H), 2.46 (m, 2H), 1.77 (m, 2H), 1.4 (m, 2H), 1.37 (t, 3H).

Ejemplo 143

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico.

487



Este compuesto se sintetiza a partir de la piperidin-4-ilamida del ácido 4-(6-metoxi-piridin-3-il)-4H-indol-2-carboxílico 181 (para la preparación, ver más adelante), y la amina 164, de una manera análoga al método descrito para el 54, seguido por la disociación del grupo protector.

MS (ESI): 504 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.48 (br s, 1H), 8.28 (d, 1H), 7.97 (d, 1H), 7.41 (d, 1H), 7.36 (s, 1H), 7.24 (dd, 1H), 7.09 (d, 1H), 6.96 (d, 1H), 4.44 (d, 1H), 3.93 (s, 3H), 3.68 - 3.82 (m, 1H), 2.61 - 2.96 (m, 6H), 2.04 - 2.39 (m, 4H), 1.85 - 1.96 (m, 2H), 1.66 - 1.82 (m, 3H), 1.45 - 1.65 (m, 2H), 1.2 - 1.44 (m, 2H), 0.91 (d, 3H), 0.86 (d, 3H).

Síntesis de piperidin-4-il-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico (181)

(1) Paso A: Terbutil-éster del ácido 4-[(4-bromo-1H-indol-2-carbonil)-amino]-piperidin-1-carboxílico (182).

Se disuelve ácido 4-bromo-1H-indol-2-carboxílico (3 gramos, 12.5 milimoles) en 30 mililitros de N,N-dimetil-formamida, y la solución se enfría a 0°C. Después de la adición de base de Hunig (6.4 mililitros, 37.5 milimoles), la mezcla se agita durante 15

minutos. Se agrega el terbutil-éster del ácido piperidin-4-il-carbámico 3 (2.5 gramos, 12.5 milimoles), seguido por PyBOP (7.2 gramos, 13.7 milimoles). La mezcla de reacción se agita durante 18 horas a temperatura ambiente. Luego se agrega acetato de etilo e hidróxido de sodio concentrado, hasta alcanzar un pH de 11. Las capas orgánicas se lavan con salmuera, se secan sobre sulfato de sodio, y se evaporan. El producto crudo se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, acetato de etilo / ciclohexano, 1:1).

Rendimiento: 5.13 gramos (97 por ciento). MS (ESI): 420, 422 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.9 (m, 1H), 8.48 (d, 1H), 7.45 (d, 1H), 7.27 (d, 1H), 7.21 (s, 1H), 7.11 (dd, 1H), 2.86 (m, 2H), 1.81 (m, 2H), 1.42 (s, 9H), 1.42 (m, 2H).

(2) Paso B: Terbutil-éster del ácido 4-{[-4-(6-metoxi-piridin-3-il)-1H-indol-2-carbonil]-amino}-piperidin-1-carboxílico (183).

Se burbujeó una corriente de argón a través de una solución del 182 anterior (500 miligramos, 1.2 milimoles), y ácido 2-metoxi-5-piridin-borónico (181 miligramos, 1.2 milimoles) en 4 mililitros de 1-propanol durante 15 minutos. Luego se agregan una solución acuosa de carbonato de sodio 2M (1.2 mililitros, 2.4 milimoles) y cloruro de bis-(trifenil-fosfina)-paladio-(II) (50 miligramos, 0.07 milimoles), y la mezcla de reacción se agita a 85°C durante 3 horas. Entonces la mezcla se enfría a 0°C, y se agrega acetato de etilo y una solución concentrada de hidróxido de sodio hasta alcanzar un pH de 11. La solución se lava con salmuera, y las capas orgánicas se secan sobre

sulfato de sodio y se evaporan. El producto crudo se purifica mediante cromatografía por evaporación (gel de sílice, ciclohexano / acetato de etilo, 7:3).

Rendimiento: 290 miligramos (69 por ciento). MS (ESI): 451.2 $[M+H]^+$, 1H-RMN ($CDCl_3$): δ (ppm) 9.3 (s, 1H), 8.53 (s, 1H), 7.96 (d, 1H), 7.46 (d, 1H), 7.38 (dd, 1H), 7.17 (d, 1H), 6.98 (s, 1H), 6.86 (d, 1H), 6.12 (d, 1H), 4.13 (m, 2H), 4.08 (s, 3H), 2.91 (m, 2H), 2.01 (m, 2H), 1.48 (s, 9H), 1.42 (m, 2H), 1.27 (m, 1H).

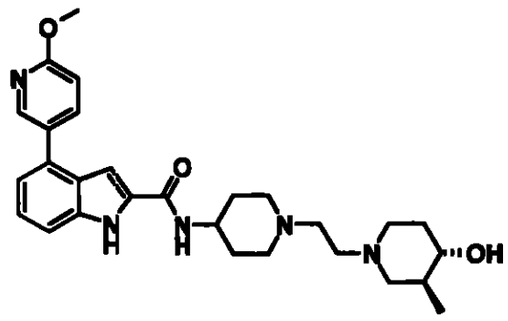
(3) Paso C: Piperidin-4-il-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico (181).

El 183 anterior (370 miligramos, 0.82 milimoles) se disuelve en una solución 4M de HCl en dioxano (7.5 mililitros, 30 milimoles), y se agita durante 1 hora a temperatura ambiente. Luego la mezcla de reacción se evapora, se disuelve en acetato de etilo, y se agrega hidróxido de sodio concentrado hasta alcanzar un pH de 11. La capa orgánica se lava con salmuera, se seca sobre sulfato de sodio, y se evapora bajo presión reducida.

Rendimiento: 300 miligramos (100 por ciento). MS (ESI): 351.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.74 (m, 1H), 8.51 (s, 1H), 8.35 (d, 1H), 8.00 (d, 1H), 7.44 (d, 1H), 7.41 (s, 1H), 7.27 (dd, 1H), 7.11 (d, 1H), 7.00 (d, 1H), 3.95 (s, 3H), 3.84 (m, 1H), 2.96 (m, 2H), 2.31 (m, 1H), 2.01 (m, 2H), 1.75 (m, 2H), 1.4 (m, 2H).

Ejemplo 144

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carb xílico.



Este compuesto se sintetiza a partir de la [1-(2-hidroxi-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico 184 (para la preparación, ver más adelante), y (3S,4S)-3-metil-piperidin-4-il-éster del ácido 2,2-dimetil-propiónico (17), de una manera análoga al método descrito en el Ejemplo 150, seguido por la disociación del grupo protector.

MS (ESI): 492 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.70 (s, 1H), 8.48 (br s, 1H), 8.30 (d, 1H), 7.97 (dd, 1H), 7.42 (d, 1H), 7.36 (s, 1H), 7.24 (t, 1H), 7.09 (d, 1H), 6.97 (d, 1H), 4.47 (d, 1H), 3.92 (s, 3H), 3.75 (m, 1H), 2.70 - 2.90 (m, 5H), 2.31 - 2.41 (m, 4H), 1.86 - 2.04 (m, 3H), 1.66 - 1.82 (m, 3H), 1.46 - 1.62 (m, 3H), 1.3 - 1.44 (m, 2H), 0.86 (d, 3H).

Síntesis de [1-(2-hidroxi-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico (184)

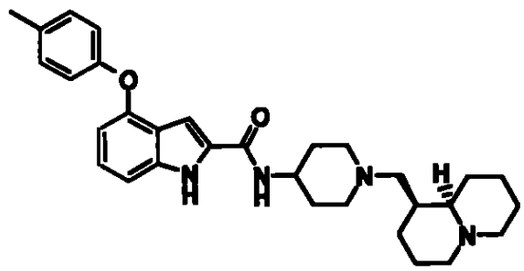
Se disuelve la piperidin-4-il-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico (181), (150 miligramos, 0.43 milimoles) en 3 mililitros de etanol bajo argón. Después de la adición de carbonato de sodio (182 miligramos, 1.7 milimoles) y 2-bromo-etanol (61 microlitros, 0.85 milimoles), la mezcla de reacción se agita a

491 #493

80°C durante 13 horas. La mezcla se diluye con cloruro de metileno, se filtra, y el filtrado se evapora. La evaporación bajo presión reducida dio 128 miligramos del producto crudo, el cual se purifica adicionalmente mediante cromatografía por evaporación (diclorometano / metanol / amoníaco al 25 por ciento (90:9:1). Rendimiento: 90 miligramos (53 por ciento). MS (ESI): 395.2 $[M+H]^+$.

Ejemplo 145

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico.



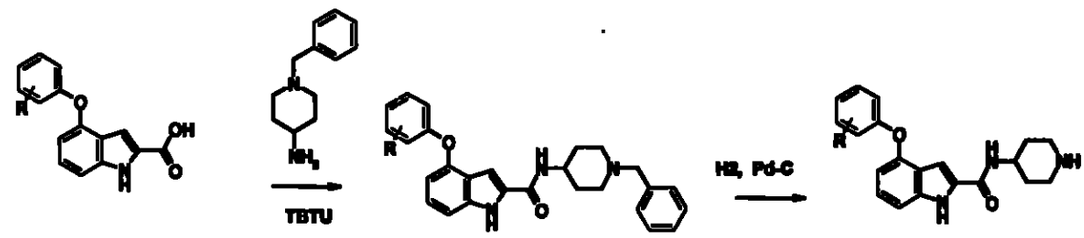
Este compuesto se sintetiza a partir del compuesto 185 (para la preparación, ver más adelante), y octahidro-2H-quinolizin-1-il-metanol, de una manera análoga al método descrito en el Ejemplo 127.

Rendimiento: 86 miligramos (34.9 por ciento). MS (ESI): 501 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.2 (d, 1H), 7.2 (d, 2H), 7.15 (d, 2H), 7.1 (s, 1H), 6.85 (d, 2H), 6.47 (d, 1H), 3.72 (m, 1H), 2.8 (dd, 2H), 2.70 (d, 2H), 2.45 (m, 1H), 2.3 (s, 3H), 2.28 (m, 1H), 2.03 (dd, 1H), 1.1 - 2.1 (m, 19H).

Síntesis de piperidin-4-il-amida del ácido 4-p-tolíloxi-1H-indol-2-carboxílico (185):

492 1497

Esquema de Reacción 18:



(1) Paso A: (1-bencil-piperidin-4-il)-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico (186).

Se disuelven ácido 4-p-toliloxi-1H-indol-2-carboxílico (137) (850 miligramos, 3.2 milimoles), y 4-amino-N-bencil-piperidina (605 miligramos, 3.2 milimoles) en 5 mililitros de N,N-dimetil-formamida, y después de la adición de TBTU (1.2 gramos, 3.5 milimoles) y etil-di-isopropil-amina (2.2 mililitros, 12.8 milimoles), la mezcla se agita a temperatura ambiente durante 2 horas. Luego la mezcla se evapora en un alto vacío. El residuo se disuelve en acetato de etilo y se lava con una solución saturada de $NaHCO_3$, y salmuera. Las capas orgánicas se secan sobre Na_2SO_4, se filtran, y se evaporan bajo presión reducida.

Rendimiento: 1.47 gramos (100 por ciento) de una espuma amarilla. MS (ESI): 438 $[M-H]^-$.

(2) Paso B: Piperidin-4-il-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico (185).

Se coloca Pd-C (1 gramo) en un matraz llenado con argón y cubierto con metanol. Se disuelve el 186 (1.4 gramos, 3.2 milimoles)

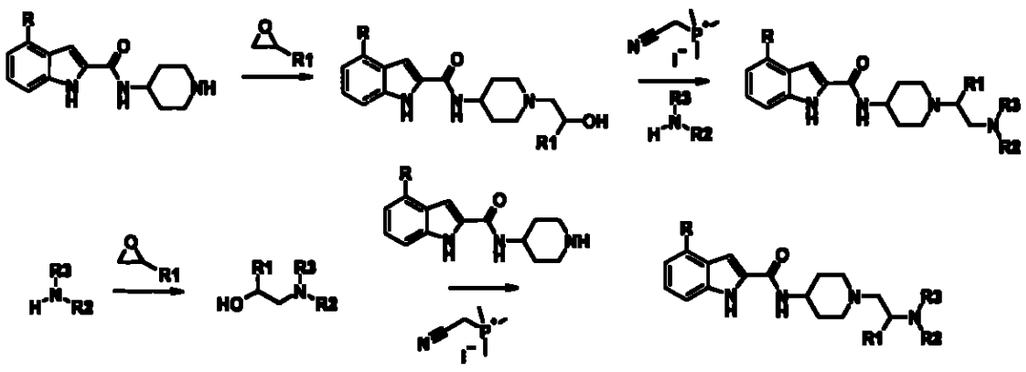
493

en 100 mililitros de metanol, y se agregan 1.6 mililitros de HCl 2M. Después de la hidrogenación a temperatura ambiente durante 5 horas, la mezcla se filtra sobre Celite y se evapora.

Rendimiento: 1.1 gramos (96 por ciento) de una espuma blanca. MS (ESI): 350 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.43 (d, 1H), 7.2 (d, 1H), 7.1 - 7.2 (m, 4H), 6.85 (d, 2H), 6.47 (d, 1H), 4.05 (m, 1H), 3.26 (m, 2H), 2.90 (m, 2H),,2.73 (s, 1H), 2.28 (s, 3H), 1.9 (m, 2H), 1.7 (m, 2H).

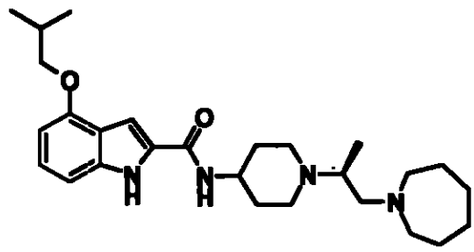
De una manera alternativa, se pudieron preparar las indol-2-carboxamidas ramificadas como se muestra en el esquema de reacción 19.

Esquema de Reacción 19:



Ejemplo 146

[1-(2-azepan-1-il-1S-metil-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico.



(1) Paso A: [1-(2R-hidroxi-propil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico (187).

Una solución del clorhidrato de piperidin-4-il-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico (161) del Ejemplo 127 (300 miligramos, 0.85 milimoles) en 5 mililitros de etanol, y trietil-amina (0.472 mililitros, 3.4 milimoles), se trata con R(+)-óxido de propileno (0.59 mililitros, 4.25 milimoles), y se agita a temperatura ambiente en un recipiente sellado durante 14 horas. Se agrega otra porción de R(+)-óxido de propileno (0.59 mililitros, 4.25 milimoles), y se continúa la agitación durante 24 horas. Luego se evaporan los solventes. El crudo se vuelve a disolver en DCM, y se lava con NaOH 2N y salmuera. La capa orgánica se seca sobre sulfato de sodio anhidro y se evapora para dar un polvo blanco.

Rendimiento: 290 miligramos (91 por ciento). MS (ESI): 374.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.22 (d, 1H), 7.22 (s, 1H), 7.03 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.25 (br s, 1H), 3.84 (d, 2H), 3.75 (m traslapado, 2H), 2.87 (m, 2H), 1.98 - 2.39 (m, 5H), 1.76 (m, 2H) 1.58 (m, 2H), 1.05 (m, 9H).

(2) Paso B: [1-(2-azepan-1-il-1S-metil-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico.

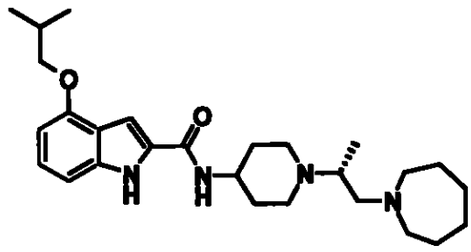
495

El alcohol (187) anterior (100 miligramos, 0.27 milimoles) se mezcla con azepano (0.033 mililitros, 0.298 milimoles), DIEA (0.227 mililitros, 1.34 milimoles), y yoduro de cianometil-trifenil-fosfonio (156 miligramos, 0.648 milimoles) en 2 mililitros de propionitrilo. La suspensión se calienta a 90°C durante 3 horas. La solución resultante se enfría, se diluye con EtOAc, se lava con NaOH 2N, y salmuera, se seca sobre sulfato de sodio anhidro, y se evapora. El material crudo se purifica mediante cromatografía sobre gel de sílice utilizando DCM (saturado con amoníaco) y MeOH (desde el 0 por ciento hasta el 10 por ciento).

Rendimiento: 74 miligramos (61 por ciento). MS (ESI): 455.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.2 (d, 1H), 7.22 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.44 (d, 1H), 3.84 (d, 2H), 3.72 (br m, 1H), 2.52 - 2.95 (m, 8H), 2.15 - 2.4 (m, 3H), 2.1 (m, 1H), 1.77 (m, 2H), 1.45 - 1.67 (m, 10H) 1.05 (d, 6H), 0.95 (d, 3H).

Ejemplo 147

[1-(2-azepan-1-il-1R-metil-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico.

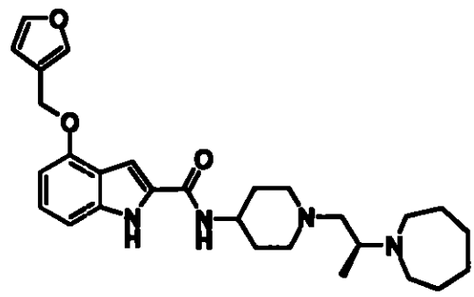


El compuesto del título se prepara como se describe en el Ejemplo 83 a partir de piperidin-4-il-amida del ácido 4-isobutoxi-1H-

indol-2-carboxílico (161), S(-)-óxido de propileno, y azepano. El intermediario de [1-(2S-hidroxi-propil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico (188) y el producto final, tuvieron espectros de MS y RMN idénticos a los de los enantiómeros-(R) del Ejemplo 146.

Ejemplo 148

[1-(2S-azepan-1-il-propil)-piperidin-4-il]-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico.



Se mezclan S(-)-óxido de propileno (21.2 mililitros, 302.5 milimoles), y azepan (3.41 mililitros, 30.25 milimoles) en 10 mililitros de etanol, y se agitan en un recipiente sellado durante 24 horas. Luego se evaporan los solventes, y se utiliza el aceite crudo de 1-azepan-1-il-propan-2S-ol (189) como tal sin mayor purificación. Rendimiento: 2.25 gramos (47 por ciento).

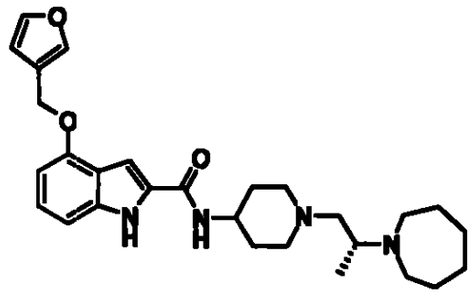
El alcohol (189) anterior (63 miligramos, 0.408 milimoles) se mezcla con la piperidin-4-il-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico 165 (ver el Ejemplo 133) del Paso B (100 miligramos, 0.27 milimoles), DIEA (0.227 mililitros, 1.35 milimoles), y yoduro de cianometil-trifenil-fosfonio (193 miligramos, 0.81

497

milimoles) en 2 mililitros de propionitrilo. La suspensión se calienta a 90°C durante 3 horas. La solución resultante se enfría, se diluye con EtOAc, se lava con NaOH 2N y salmuera, se seca sobre sulfato de sodio anhidro, y se evapora. El material crudo se purifica mediante cromatografía sobre gel de sílice utilizando DCM (saturado con amoniaco) y MeOH (desde el 0 por ciento hasta el 10 por ciento). Rendimiento: 45 miligramos (35 por ciento). MS (ESI): 479.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.46 (s, 1H), 8.14 (d, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.22 (s, 1H), 7.05 (t, 1H), 6.99 (d, 1H), 6.62 (s, 1H), 6.59 (d, 1H), 5.03 (d, 2H), 3.72 (m, 1H), 2.75 - 2.95 (m, 3H), 2.58 (m, 4H), 2.33 (m, 1H), 2.0 - 2.2 (m, 2H), 1.92 (m, 1H), 1.74 (m, 2H), 1.45 - 1.6 (m, 10H), 0.91 (d, 3H).

Ejemplo 149

[1-(2R-azepan-1-il-propil)-piperidin-4-il]-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico.



El compuesto del título se prepara a partir de piperidin-4-il-amida del ácido 4-(furan-3-il-metoxi)-1H-indol-2-carboxílico (165), como se describe en el Ejemplo 133, utilizando R(+)-óxido de propileno en lugar del enantiómero-(S).

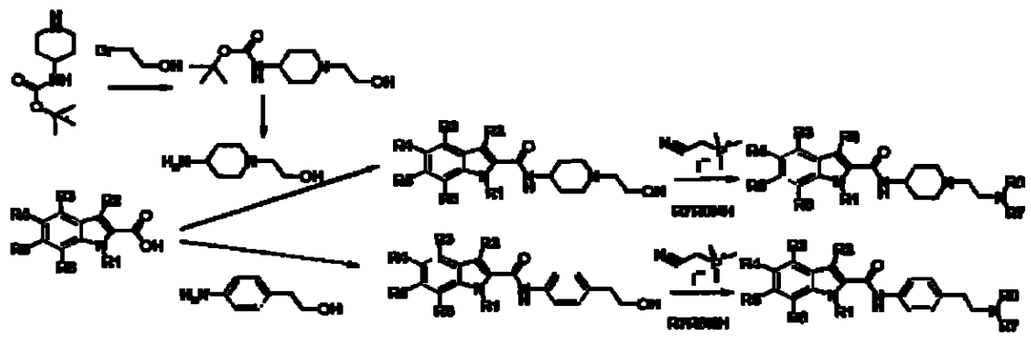
Los espectros de MS Y RMN son idénticos a los de su ejemplo

498 500

enantiomérico 148.

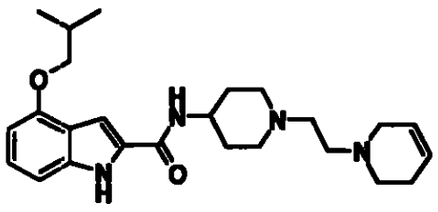
De una manera alternativa, las 4-alcoxi-indol-2-carboxamidas se preparan como se muestra en el esquema de reacción 20.

Esquema de Reacción 20:



Ejemplo 150

{1-[2-(3,6-dihidro-2H-piridin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico.



Se agregan subsecuentemente 1,2,5,6-tetrahidro-piridina (25.4 microlitros, 0.279 milimoles), yoduro de ciano-metil-trifenil-fosfonio (162.5 miligramos, 0.6686 milimoles), y base de Hünig (171 microlitros, 1 milimol), a una suspensión del 190 (para la preparación, ver más adelante) (100 miligramos, 0.279 milimoles) en 4 mililitros de propionitrilo. La mezcla se agita durante 2 horas a

100°C, luego se diluye con acetato de etilo, se lava con una solución de hidróxido de sodio 1N y salmuera, y se seca sobre sulfato de sodio. La evaporación dio 138 miligramos del producto crudo, el cual se purifica adicionalmente mediante HPLC de preparación (RP, acetonitrilo / agua).

Rendimiento: 55 miligramos (47 por ciento). MS (ESI): 443.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H), 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Síntesis de [1-(2-hidroxi-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico (190)

(1) Paso A: Terbutil-éster del ácido [1-(2-hidroxi-etil)-piperidin-4-il]-carbámico (191).

Se disuelve terbutil-éster del ácido piperidin-4-il-carbámico (5 gramos, 25 milimoles) en 100 mililitros de etanol. Después de la adición de carbonato de sodio (10.6 gramos, 100 milimoles), se agrega por goteo 2-bromo-etanol (3.55 mililitros, 50 milimoles). La mezcla de reacción se pone a reflujo durante 16 horas, y luego se evapora. El residuo se disuelve en 100 mililitros de diclorometano, y se filtra. El residuo se lava con DCM. Los filtrados combinados se evaporan, lo cual proporciona 10.1 gramos de un aceite amarillo, el cual se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, DCM / metanol / amoníaco concentrado,

90:9:1).

Rendimiento: 4.02 gramos (66 por ciento) de un sólido blanco. MS (ESI): 443.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

(2) Paso B: 2-(4-amino-piperidin-1-il)-etanol (192).

El compuesto 191 (4.02 gramos, 16.46 milimoles) se trata con HCl 4M en dioxano (60 mililitros, 240 milimoles), y la mezcla se agita a temperatura ambiente durante 1 hora. El precipitado blanco se filtra, se lava con éter, y se seca bajo un alto vacío. El licor madre se concentra y se trata con éter. El sólido blanco se filtra y se seca bajo un alto vacío.

Rendimiento: 3.42 gramos (95.9 por ciento). MS (ESI): 443.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

(3) Paso C: [1-(2-hidroxi-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico (190).

El ácido 4-isobutoxi-1H-indol-2-carboxílico 80 (para la preparación, ver el Ejemplo 8, 1 gramo, 4.29 milimoles) se suspende en 5 mililitros de N,N-dimetil-formamida, se enfría a 0°C, y se trata

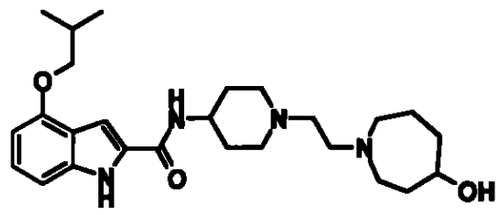
501

con base de Hünig (1.46 mililitros, 8.58 milimoles). La mezcla se agita durante 15 minutos a 0°C. En un matraz de reacción separado, el compuesto 192 (931 miligramos, 4.29 milimoles) en 10 mililitros de N,N-dimetil-formamida se enfría a 0°C, se trata con una solución acuosa de hidróxido de sodio 10M (0.858 mililitros, 8.58 milimoles), y se agita durante 15 minutos a esta temperatura. Esta solución se agrega a la mezcla anteriormente mencionada, seguida por hexafluorofosfato de benzotriazol-1-il-oxi-tri-pirrolidin-fosfonio (PyBOP, 2.34 gramos, 4.5 milimoles), y se agita durante 4 horas a temperatura ambiente. La mezcla de reacción se diluye con acetato de etilo y se lava con una solución de hidróxido de sodio 2N, agua, y salmuera. La evaporación dio un producto crudo amarillo semisólido, el cual se trata con éter, se filtra, y se lava con éter.

Rendimiento: 657 miligramos (83 por ciento). MS (ESI): 443.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.2 (d, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 6.97 (d, 1H), 6.45 (d, 1H), 4.5 (d, 1H), 3.85 (d, 2H) 3.74 (m, 1H), 3.41 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H), 2.38 (m, 4H), 2.1 (m, 1H), 2.0 (m, 4H), 1.76 (m, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H).

Ejemplo 151

{1-[2-(4-hidroxi-azepan-1-il)-etil]-piperidin-4-il}-amida del ácid 4-isobutoxi-1H-indol-2-carboxílico.



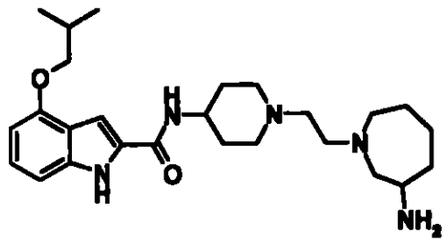
502 804

Este compuesto se sintetiza de una manera análoga al Ejemplo 150, a partir de [1-(2-hidroxi-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico 190, y azepan-4-ol.

Rendimiento: 36 miligramos (60 por ciento). MS (ESI): 457 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.19 (d, 1H), 7.23 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.44 (d, 1H), 4.35 (d, 1H), 3.84 (d, 2H), 3.80 - 3.62 (m, 2H), 3.29 (s, 1H), 2.88 (d, 2H), 2.68 - 2.30 (m, 8H), 2.14 - 2.06 (m, 1H), 2.0 (t, 2H), 1.83 - 1.34 (m, 9H), 1.05 (d, 6H).

Ejemplo 152

{1-[2-(3-amino-azepan-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutil-1H-indol-2-carboxílico.



Este compuesto se sintetiza de una manera análoga al Ejemplo 150, a partir de [1-(2-hidroxi-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico 190, y azepan-3-il-amina.

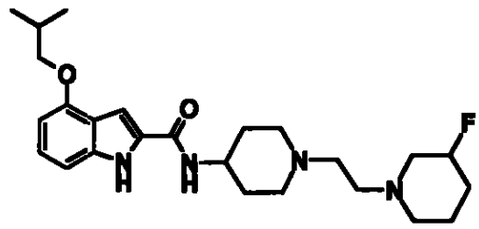
Rendimiento: 48 miligramos (38 por ciento). MS (ESI): 456.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.5 (s, 1H), 8.27 (d, 1H), 7.24 (s, 1H), 7.05 (t, 1H), 6.97 (d, 1H), 6.46 (d, 1H), 3.84 (d, 2H), 3.80 - 3.70 (m, 1H), 2.89 (m, 2H), 2.79 (m, 1H), 2.68 - 2.62 (m, 1H), 2.60 - 2.52 (m,

503

4H), 2.43 - 2.27 (m, 3H), 2.15 - 2.05 (m, 1H), 2.05 - 1.95 (m, 2H), 1.78 - 1.72 (m, 2H), 1.70 - 1.68 (m, 2H), 1.60 - 1.50 (m, 6H), 1.43 - 1.35 (m, 1H), 1.32 - 1.22 (m, 1H), 1.05 (d, 6H).

Ejemplo 153

{1-[2-(3-fluoro-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutil-1H-indol-2-carboxílico.



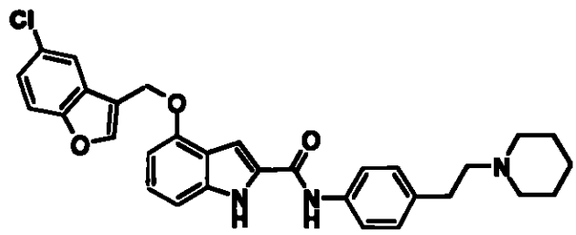
A una suspensión del 190 (ver el Ejemplo 150) (100 miligramos, 0.28 milimoles), clorhidrato de 3-fluoropiperidina (43 miligramos, 0.208 milimoles), y DIEA (0.189 mililitros, 1.12 milimoles) en 0.5 mililitros de propionitrilo, se le agrega yoduro de ciano-metil-trifenil-fosfonio (81 miligramos, 0.336 milimoles). La mezcla se calienta a 90°C durante 14 horas. Luego la solución resultante se diluye con EtOAc (20 mililitros), y se lava dos veces con bicarbonato de sodio saturado, se seca sobre sulfato de sodio, y se evapora. El producto crudo se purifica adicionalmente mediante HPLC de preparación.

Rendimiento: 30 miligramos (24 por ciento). MS (ESI): 445.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.43 (s, 1H), 8.19 (d, 1H), 7.22 (s, 1H), 7.02 (t, 1H), 6.96 (d, 1H), 6.45 (d, 1H), 4.45 - 4.7 (m, 1H), 3.84 (d, 2H), 3.74 (m, 1H), 2.88 (m, 2H), 2.76 (m, 1H), 2.18 - 2.48 (m,

8H), 2.1 (m, 1H), 2.0 (m, 2H), 1.34 - 1.9 (m, 7H), 1.05 (d, 6H).

Ejemplo 154

[4-(2-piperidin-1-il-etil)-fenil]-amida del ácido 4-(5-cloro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico.



Este compuesto se sintetiza de una manera análoga al Ejemplo 150, a partir de [4-(2-hidroxi-etil)-fenil]-amida del ácido 4-(5-clorobenzofuran-3-il-metoxi)1H-indol-2-carboxílico 193 (para la preparación, ver más adelante), y piperidina.

Rendimiento: 140 miligramos (67 por ciento). MS (ESI): 528/530 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.69 (s, 1H), 10.00 (s, 1H), 8.28 (s, 1H), 7.85 - 7.35 (m, 6H), 7.25 - 7.00 (m, 4H), 6.75 (d, 1H), 5.40 (2, 2H), 2.70 (m, 4H), 2.60 - 2.20 (m, 4H), 1.55 - 1.40 (m, 6H).

Síntesis de [4-(2-hidroxi-etil)-fenil]-amida del ácido 4-(5-cloro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico (193)

Este compuesto se sintetiza de una manera análoga al Ejemplo 42, a partir del ácido 4-(5-cloro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico (97) y 2-(4-amino-fenil)-etanol.

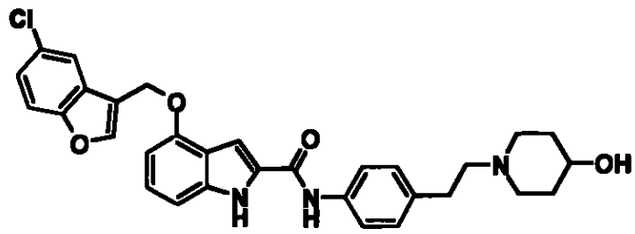
Rendimiento: 1.59 gramos (69 por ciento) de un sólido blanco. MS (ESI): 461/463 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.68 (s, 1H), 9.99 (s, 1H), 8.27 (s, 1H), 7.80 (d, 1H), 7.70 - 7.60 (m, 3H), 7.46 (d,

505 507

1H), 7.39 (dd, 1H), 7.20 - 7.10 (m, 3H), 7.06 (d, 1H), 6.75 (d, 1H), 5.37 (s, 2H), 4.59 (m, 1H), 3.57 (m, 2H), 2.67 (t, 2H).

Ejemplo 155

{4-[2-(4-hidroxi-piperidin-1-il)-etil]-fenil}-amida del ácido 4-(5-cloro-benzofuran-3-il-metoxi)-1H-indol-2-carboxílico.



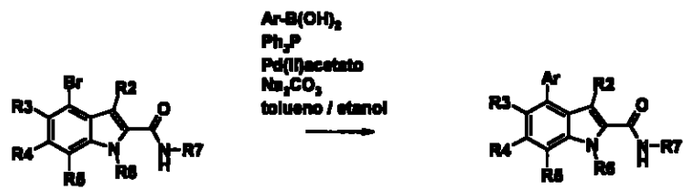
Este compuesto se sintetiza de una manera análoga al Ejemplo 154, a partir de [4-(2-hidroxi-etil)-fenil]-amida del ácido 4-(5-clorobenzofuran-3-il-metoxi)1H-indol-2-carboxílico (193), y piperidin-4-il-éster del ácido 2,2-dimetil-propiónico, seguido por la remoción del grupo protector mediante el metilato de sodio.

Rendimiento: 38 miligramos (34.9 por ciento). MS (ESI): 528/530 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.68 (s, 1H), 8.27 (s, 1H), 7.63 (d, 1H), 7.70 - 7.60 (m, 3H), 7.45 (d, 1H), 7.38 (dd, 1H) (s, 1H), 7.20 - 7.00 (m, 4H), 6.75 (d, 1 H), 5.37 (s, 2H), 4.49 (d, 1H), 3.42 (m, 1H), 2.80 - 2.60 (m, 4H), 2.45 - 2.40 (m, 1H), 2.10 - 1.95 (m, 3H), 1.75 - 1.65 (m, 2H), 1.45-1.30 (m, 2H).

La 4-aril-indol-2-carboxamidas se preparan en general mediante un acoplamiento de Suzuki de las 4-bromo-indol-2-carboxamidas con los ácidos aril-borónicos correspondientes (Esquema de Reacción 15).

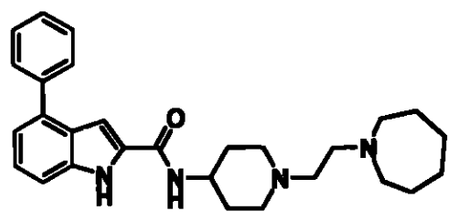
566 308

Esquema de Reacción 21:



Ejemplo 166

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-fenil-1H-indol-2-carboxílico.



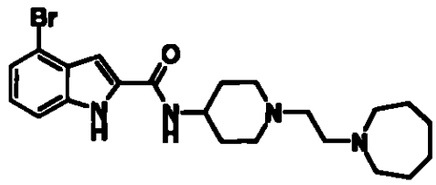
Se disuelven bromindol 194 (para la preparación, ver más adelante) (150 miligramos, 0.335 milimoles), ácido fenil-borónico (82 miligramos, 0.67 milimoles), y trifenil-fosfina (26.4 miligramos, 0.112 milimoles), en 10 mililitros de tolueno. Después de la adición de 1 mililitro de etanol, se inyecta argón a través de la mezcla durante 30 minutos. Luego se agregan acetato de Pd (II) (3 miligramos, 13.4 micromoles), y carbonato de sodio acuoso 2M (0.67 mililitros, 1.34 milimoles). La mezcla se agita bajo reflujo durante 3 horas. Después de enfriarse a temperatura ambiente, la mezcla se trata con 30 mililitros de acetato de etilo, y una solución acuosa de $NaHCO_3$ al 5 por ciento, y se filtra sobre Celite. La capa orgánica se separa, y la evaporación bajo presión reducida dio 170 miligramos del producto

507 509

crudo, el cual se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, acetato de etilo / metanol, NH_3 concentrado, 90:10:2), y mediante cristalización a partir de acetato de etilo.

Rendimiento: 45 miligramos (30 por ciento) de un sólido blanco; MS (ESI): 445.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.64 (s, 1H), 8.25 (d, 1H), 7.63 (d, 2H), 7.50 (dd, 2H), 7.40 (m, 2H), 7.31 (s, 1H), 7.23 (dd, 1H), 7.08 (d, 1H), 3.73 (m, 1H), 2.85 (m, 2H), 2.57 (m, 6H), 2.36 (m, 2H), 1.99 (m, 2H), 1.74 (m, 2H), 1.52 (m, 10H).

(1) [1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-bromo-1H-indol-2-carboxílico (194).



Se disuelven ácido 4-bromo-1H-indol-2-carboxílico (1.5 gramos, 3.1 milimoles), triclorhidrato de 1-(2-azepan-1-il-etil)-piperidin-4-il-amina (5) (2.1 gramos, 3.1 milimoles), y DIEA (4.3 mililitros, 12.4 milimoles), bajo una atmósfera de argón, en N,N-dimetilformamida (25 mililitros). Se agrega TBTU (2.3 gramos, 3.4 milimoles) a temperatura ambiente. La mezcla de reacción se agita durante 2 horas a temperatura ambiente, se evapora bajo un alto vacío, se disuelve en acetato de etilo, y se lava dos veces con una solución acuosa de $NaHCO_3$ al 5 por ciento. Las capas orgánicas se secan sobre sulfato de sodio. La evaporación bajo presión reducida

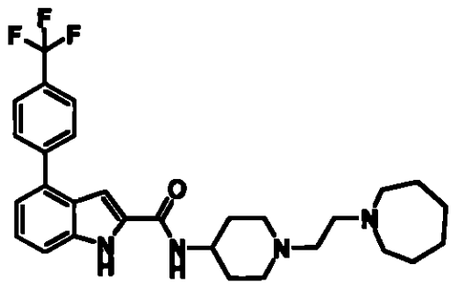
508 510

dio 1.3 gramos (93 por ciento) de un sólido beige.

MS (ESI): 447.1, 449.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.4 (d, 1H), 7.4 (d, 1H), 7.25 (d, 1H), 7.2 (s, 1H), 7.08 (dd, 1H), 3.76 (m, 1H), 2.88 (m, 2H), 2.55 - 2.68 (m, 6H), 2.4 (m, 2H), 2.05 (m, 2H), 1.78 (m, 2H), 1.5 - 1.62 (m, 10H).

Ejemplo 157

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-trifluorometil-fenil)-1H-indol-2-carboxílico.



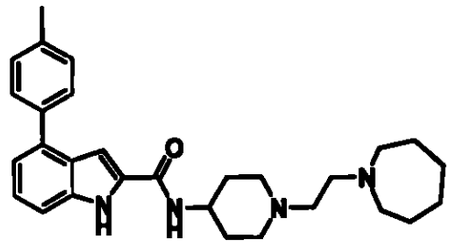
Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 146) y ácido 4-trifluorometil-fenil-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 35 miligramos (20 por ciento) de cristales blancos; MS (ESI): 513 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.25 (d, 1H), 7.85 (s, 4H), 7.48 (d, 1H), 7.32 (s, 1H), 7.28 (dd, 1H), 7.15 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5 - 2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.78 (m, 2H), 1.48 - 1.55 (m, 10H).

Ejemplo 158

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-p-tolil-1H-indol-2-carboxílico.

559 5tA

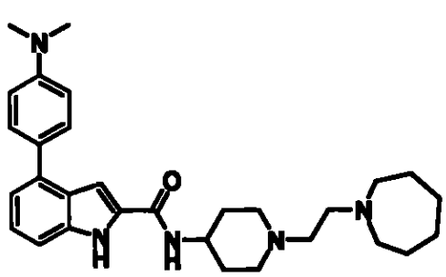


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido 4-p-tolil-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 40 miligramos (26 por ciento) de una espuma blanca; MS (ESI): 459 $[M+H]^+$, 1 H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.53 (d, 2H), 7.48 (d, 1H), 7.32 (d, 2H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 1H), 3.75 (m, 1H), 2.5 - 2.6 (m, 8H), 2.38 (s, 3H), 2.33 - 2.4 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48 - 1.55 (m, 10H).

Ejemplo 159

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-dimetilamino-fenil)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido (4-dimetilamino-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

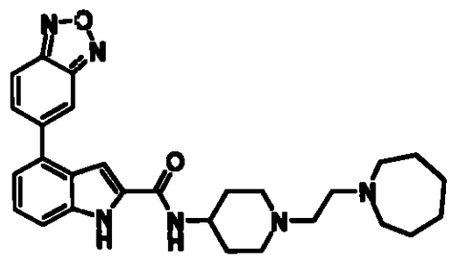
Rendimiento: 45 miligramos (28 por ciento) de una espuma blanca;

510

MS (ESI): 488.2 $[M+H]^+$, 1 H-RMN (DMSO-d_6): δ (ppm) 11.55 (s, 1H), 8.25 (d, 1H), 7.3 - 7.4 (m, 2H), 7.15 - 7.25 (m, 3H), 7.07 (m, 2H), 3.8 (s, 3H), 3.78 (s, 3H), 3.75 (m, 1H), 2.88 (m, 2H), 2.57 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.5 (m, 4H), 1.75 (m, 10H).

Ejemplo 160

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benzo[1,2,5]oxadiazol-5-il-1H-indol-2-carboxílico.

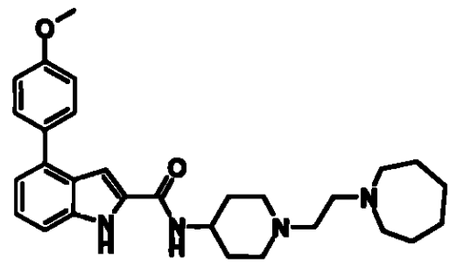


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido benzo[1,2,5]oxadiazol-5-il-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 85 miligramos (39 por ciento) de cristales blancos; MS (ESI): 487.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.8 (s, 1H), 8.3 (d, 1H), 8.2 (s, 1H), 8.18 (d, 1H), 7.95 (d, 1H), 7.52 (m, 1H), 7.38 (s, 1H), 7.3 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5 - 2.6 (m, 6H), 2.36 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47 - 1.58 (m, 10H).

Ejemplo 161

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico.

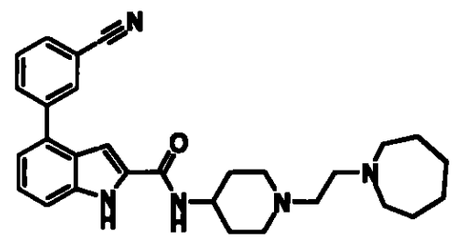


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido (4-metoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 22 miligramos (38 por ciento) de una espuma blanca; MS (ESI): 475.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.59 (s, 1H), 8.23 (d, 1H), 7.49 (d, 2H), 7.32 (m, 2H), 7.18 (dd, 1H), 7.0 (d, 1H), 6.85 (d, 2H), 3.75 (m, 1H), 2.97 (s, 6H), 2.87 (m, 2H), 2.56 (m, 6H), 2.48 (m, 2H), 2.0 (m, 2H), 1.77 (m, 2H), 1.52 (m, 10H).

Ejemplo 162

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3-cian -fenil)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido 3-ciano-fenil-borónico, de una manera análoga al método descrito en el Ejemplo 156.

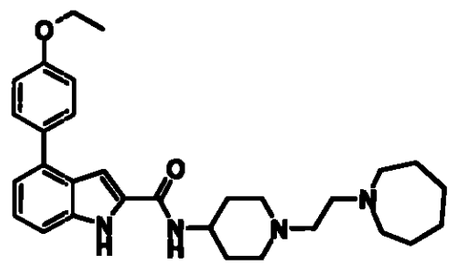
Rendimiento: 115 miligramos (55 por ciento) de cristales blancos; MS

512

(ESI): 470.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.75 (s, 1H), 8.38 (d, 1H), 8.05 (s, 1H), 7.98 (dd, 1H), 7.88 (m, 1H), 7.72 (dd, 1H), 7.47 (d, 1H), 7.3 (d, 1H), 7.25 (d, 1H), 7.15 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48 - 2.6 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47 - 1.58 (m, 10H).

Ejemplo 163

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico.



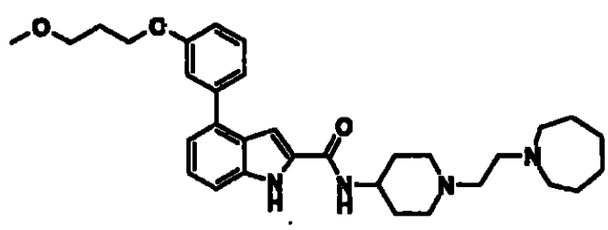
Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido (4-etoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 40 miligramos (24 por ciento) de cristales beiges; MS (ESI): 487 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.57 (d, 2H), 7.38 (d, 1H), 7.32 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1 H), 4.07 (q, 2H), 3.75 (m, 1H), 2.85 (m, 2H), 2.50 - 2.58 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48 - 1.58 (m, 8H), 1.38 (t, 3H).

Ejemplo 164

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-[3-(3-metoxi-propoxi)-fenil]-1H-ind l-2-carboxílic .

513

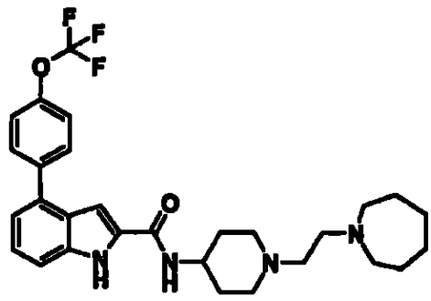


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido [3-(3-metoxi-propoxi)-fenil]-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 160 miligramos (67 por ciento) de una espuma beige; MS (ESI): 533.2 $[M+H]^+$, 1H-RMN (DMSO-d^6): δ (ppm), 11.65 (s, 1H), 8.28 (d, 1H), 7.38 - 7.43 (m, 2H), 7.32 (s, 1H), 7.2 - 7.25 (m, 2H), 7.15 (m, 1H), 7.08 (d, 1H), 6.95 (dd, 1H), 4.1 (t, 2H), 3.75 (m, 1H), 3.48 (t, 2H), 3.25 (s, 3H), 2.85 (m, 2H), 2.48 - 2.58 (m, 8H), 2.35 (m, 2H), 1.95 - 2.04 (m, 4H), 1.75 (m, 2H), 1.48 - 1.6 (m, 10H).

Ejemplo 165

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-trifluorometoxi-fenil)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido 4-trifluorometoxi-fenil-borónico, de una manera

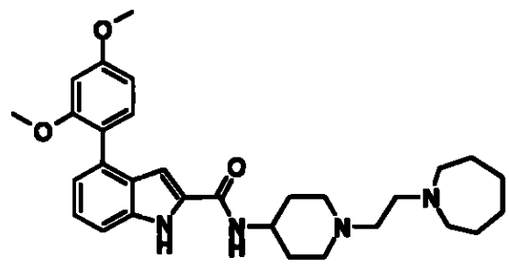
514 516

análoga al método descrito en el Ejemplo 156.

Rendimiento: 75 miligramos (42 por ciento) de una espuma blanca; MS (ESI): 529 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.7 (s, 1H), 8.28 (d, 1H), 7.78 (d, 2H), 7.50 (d, 2H), 7.44 (d, 1H), 7.3 (s, 1H), 7.25 (dd, 1H), 7.08 (d, 1H), 3.75 (m, 1H), 2.87 (m, 2H), 2.5 - 2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48 - 1.6 (m, 10H).

Ejemplo 166

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(2,4-dimetoxi-fenil)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido (2,4-dimetoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

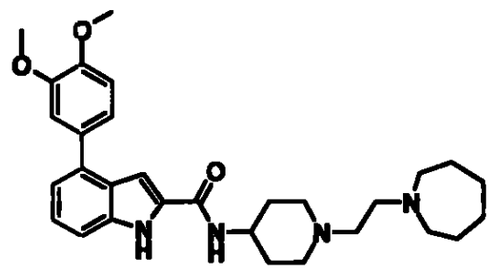
Rendimiento: 120 miligramos (53 por ciento) de una espuma beige; MS (ESI): 505.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.45 (s, 1H), 8.15 (d, 1H), 7.34 (d, 1H), 7.2 (d, 1H), 7.15 (dd, 1H), 6.93 (d, 1H), 6.9 (d, 1H), 6.7 (d, 1H), 6.65 (dd, 1H), 3.84 (s, 3H), 3.73 (m, 1H), 3.68 (s, 3H), 2.85 (m, 2H), 2.47 - 2.58 (m, 8H), 2.35 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.47 - 1.58 (m, 8H).

Ejemplo 167

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,4-

515

dimetoxi-fenil)-1H-indol-2-carboxílico.

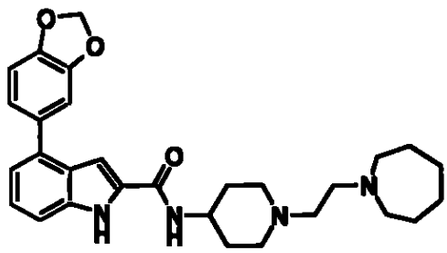


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido (3,4-dimetoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 65 miligramos (29 por ciento) de cristales blancos; MS (ESI): 505.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.3 - 7.4 (m, 2H), 7.15 - 7.25 (m, 3H), 7.07 (m, 2H), 3.8 (s, 3H), 3.78 (s, 3H), 3.75 (m, 1H), 2.88 (m, 2H), 2.57 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.5 (m, 4H), 1.75 (m, 10H).

Ejemplo 168

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benzo[1,3]dioxol-5-il-1H-indol-2-carboxílico.

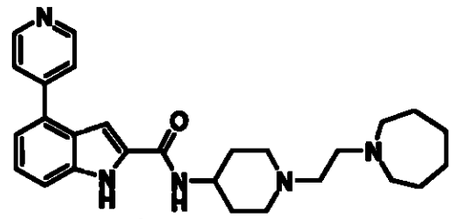


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido benzo[1,3]dioxol-5-il-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 75 miligramos (34 por ciento) de cristales blancos; MS (ESI): 489.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.28 (d, 1H), 7.38 (d, 1H), 7.3 (m, 1H), 7.2 (d, 1H), 7.18 (m, 1H), 7.1 (dd, 1H), 7.04 (dd, 1H), 6.08 (s, 2H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48 - 2.6 (m, 6H), 2.37 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47 - 1.58 (m, 10H).

Ejemplo 169

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-piridin-4-il-1H-indol-2-carboxílico.

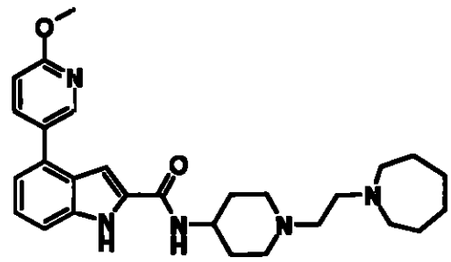


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido piridin-4-il-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 35 miligramos (53 por ciento) de cristales beiges; MS (ESI): 446.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.8 (s, 1H),.8.68 (d, 2H), 8.3 (d, 1H), 7.68 (d, 1H), 7.5 (d, 1H), 7.38 (s, 1H), 7.3 (m, 1H), 7.2 (d, 1H), 3.75 (m, 1H), 2.88 (m, 2H), 2.45 - 2.6 (m, 6H), 2.38 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.48 - 1.6 (m, 10H).

Ejemplo 170

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico.

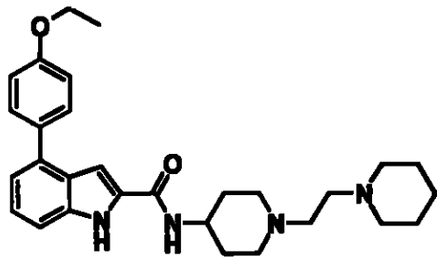


Este compuesto se sintetiza a partir del compuesto 194 (ver el Ejemplo 156) y ácido (6-metoxi-piridin-3-il)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 125 miligramos (59 por ciento) de cristales blancos; MS (ESI): 476.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.65 (s, 1H), 8.48 (d, 1H), 8.3 (d, 1H), 7.98 (dd, 1H), 7.42 (d, 1H), 7.35 (s, 1H), 7.24 (dd, 1H), 7.08 (d, 1H), 6.97 (d, 1H), 3.93 (s, 3H), 3.75 (m, 1H), 2.87 (m, 2H), 2.48 - 2.6 (m, 6H), 2.35 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47 - 1.58 (m, 10H).

Ejemplo 171

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico.

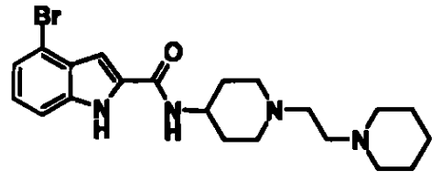


Este compuesto se sintetiza a partir del compuesto 195 (para la preparación, ver más adelante) y ácido (4-etoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

518

Rendimiento: 100 miligramos (46 por ciento) de cristales amarillos; MS (ESI): 475 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.08 (q, 2H), 3.73 (m, 1H), 2.87 (m, 2H), 2.25 - 2.4 (m, 8H), 2.0 (m, 2H), 1.75 (m, 2H), 1.3 - 1.57 (m, 8H), 1.38 (t, 3H).

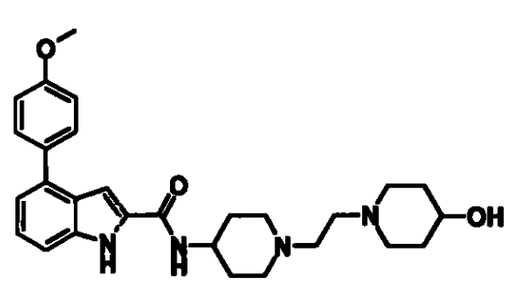
(1) [1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-bromo-1H-indol-2-carboxílico (195).



Este compuesto se sintetiza a partir del ácido 4-bromo-1H-indol-2-carboxílico, y la amina 4, de una manera análoga al método descrito anteriormente para la síntesis del 194 (ver el Ejemplo 156). MS (ESI): 433, 435 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.4 (d, 1H), 7.4 (d, 1H), 7.23 (d, 1H), 7.19 (s, 1H), 7.08 (dd, 1H), 3.76 (m, 1H), 2.88 (m, 2H), 2.3 - 2.4 (m, 8H), 2.0 (m, 2H), 1.78 (m, 2H), 1.3 - 1.6 (m, 8H).

Ejemplo 172

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico.

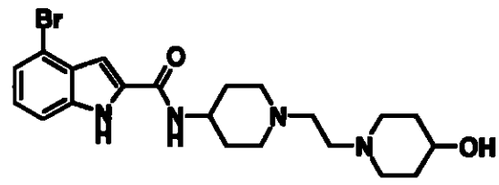


519

Este compuesto se sintetiza a partir del compuesto 196 (para la preparación, ver más adelante), y ácido (4-metoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 55 miligramos (35 por ciento) de una espuma blanca; MS (ESI): 477.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.58 (d, 2H), 7.36 (d, 1H), 7.3 (s, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.55 (br, 1H), 3.85 (s, 3H), 3.78 (m, 1H), 3.45 (m, 1H), 2.9 (m, 2H), 2.78 (m, 2H), 2.45 (m, 4H), 2.15 (m, 2H), 2.05 (m, 2H), 1.3 - 1.8 (m, 8H).

(1) {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}amida del ácido 4-bromo-1H-indol-2-carboxílico (196).



Este compuesto se sintetiza a partir del ácido 4-bromo-1H-indol-2-carboxílico y la amina 21, de una manera análoga al método descrito para el 194 (ver el Ejemplo 156).

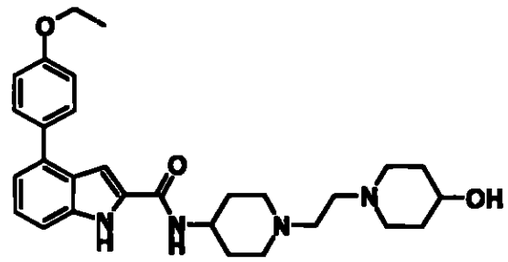
MS (ESI): 449 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.9 (s, 1H), 8.42 (d, 1H), 7.4 (d, 1H), 7.23 (d, 1H), 7.2 (s, 1H), 7.08 (dd, 1H), 3.8 (m, 1H), 3.5 (m, 1H), 2.88 (m, 2H), 2.95 (m, 2H), 2.86 (m, 2H), 2.6 (m, 2H), 2.52 (m, 2H), 2.3 (m, 2H), 2.12 (m, 2H), 1.8 (m, 2H), 1.75 (m, 2H), 1.58 (m, 2H), 1.43 (m, 2H).

Ejemplo 173

{1-[2-(4-hidr xi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido

520

4-(4-etoxi-fenil)-1H-indol-2-carboxílic .

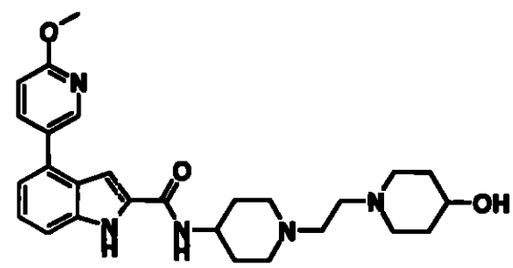


Este compuesto se sintetiza a partir del compuesto 196 (ver el Ejemplo 172) y ácido (4-etoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 45 miligramos (21 por ciento) de cristales blancos; MS (ESI): 491 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.24 (d, 1H), 7.54 (d, 2H), 7.34 (d, 1H), 7.3 (s, 1H), 7.19 (dd, 1H), 7.06 (d, 2H), 7.0 (d, 1H), 4.47 (d, 1H), 4.08 (q, 2H), 3.73 (m, 1H), 3.40 (m, 1H), 2.85 (m, 2H), 2.68 (m, 2H), 2.36 (m, 4H), 1.98 (m, 4H), 1.74 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.37 (t, 3H), 1.32 (m, 2H).

Ejemplo 174

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácid 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 196 (ver el Ejemplo 172) y ácido (6-metoxi-piridin-3-il)-borónico, de una manera

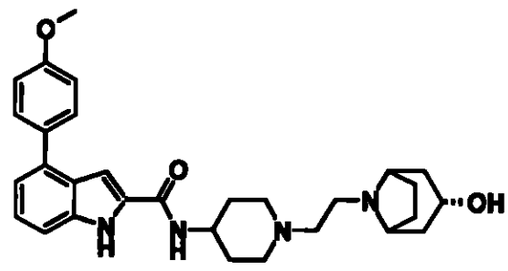
521

análoga al método descrito en el Ejemplo 156.

Rendimiento: 28 miligramos (18 por ciento) de cristales blancos; MS (ESI): 478.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.68 (s, 1H), 8.47 (d, 1H), 8.27 (d, 1H), 7.95 (dd, 1H), 7.40 (d, 1H), 7.35 (s, 1H), 7.23 (dd, 1H), 7.09 (d, 1H), 6.97 (d, 1H), 4.48 (d, 1H), 3.92 (s, 3H), 3.75 (m, 1H), 3.39 (m, 1H), 2.85 (m, 2H), 2.68 (m, 2H), 2.36 (m, 4H), 1.99 (m, 4H), 1.75 (m, 2H), 1.65 (m, 2H), 1.54 (m, 2H), 1.35 (m, 2H).

Ejemplo 175

{1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico.



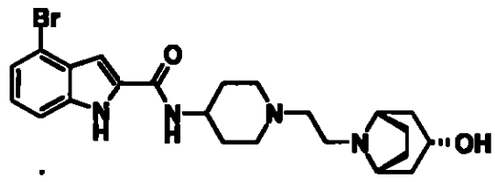
Este compuesto se sintetiza a partir del compuesto 197 (para la preparación, ver más adelante), y ácido (4-metoxi-fenil)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

Rendimiento: 90 miligramos (57 por ciento) de una espuma blanca; MS (ESI): 503.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.25 (d, 1H), 7.55 (d, 2H), 7.35 (d, 1H), 7.3 (m, 1H), 7.2 (dd, 1H), 7.05 (d, 2H), 7.02 (d, 1H), 4.25 (br s, 1H), 3.82 (s, 3H), 3.78 (m, 1H), 3.75 (m, 1H), 3.1 (m, 2H), 2.88 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.85 (m, 2H), 1.77 (m, 4H), 1.55 (m, 4H).

(1) **{1-[2-(3-hidr xi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-**

522

il}-amida del ácid 4-bromo-1H-indol-2-carboxílico (197).

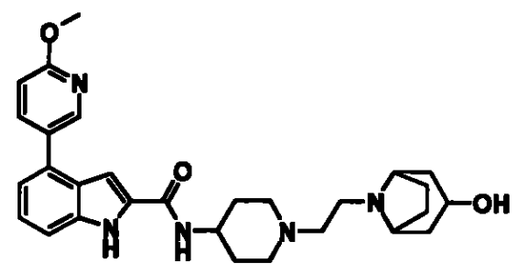


Este compuesto se sintetiza a partir del ácido 4-bromo-1H-indol-2-carboxílico y la amina 24, de una manera análoga al método descrito para el 194 (ver el Ejemplo 156).

MS (ESI): 475.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.7 (br s, 1H), 8.28 (br s, 1H), 7.49 (d, 1H), 7.25 (d, 1H), 7.15 (s, 1H), 7.1 (dd, 1H), 4.1 (br s, 1H), 3.97 (m, 3H), 3.5 (m, 2H), 3.0 (m, 2H), 2.5 (m, 6H), 1.9 - 2.2 (m, 10H).

Ejemplo 176

{1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 197 (ver el Ejemplo 175) y ácido (6-metoxi-piridin-3-il)-borónico, de una manera análoga al método descrito en el Ejemplo 156.

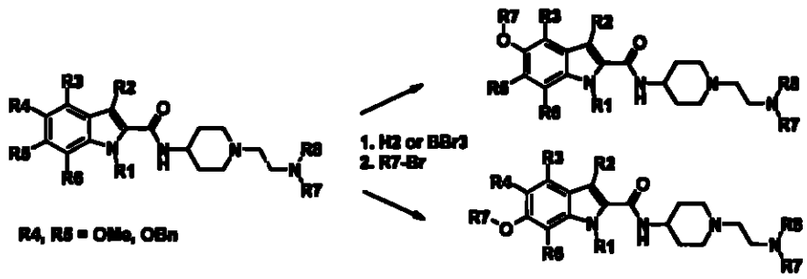
Rendimiento: 90 miligramos (57 por ciento) de una espuma blanca;

523 523

MS (ESI): 504.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 11.6 (s, 1H), 8.48 (d, 1H), 8.28 (d, 1H), 7.97 (dd, 1H), 7.4 (d, 1H), 7.35 (m, 1H), 7.23 (dd, 1H), 7.08 (d, 1H), 6.95 (d, 1H), 4.23 (br, 1H), 3.93 (s, 3H), 3.78 (m, 1H), 3.75 (m, 1H), 3.1 (m, 2H), 2.88 (m, 2H), 2.38 (m, 4H), 2.0 (m, 4H), 1.8 (m, 6H), 1.53 (m, 4H).

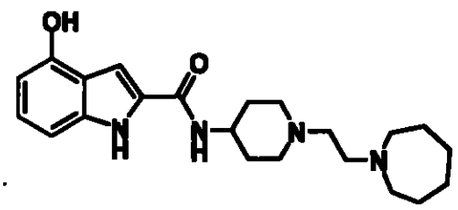
De una manera alternativa, las 4-alcoxi-indol-2-carboxamidas se preparan como se muestra en el Esquema de Reacción 22.

Esquema de Reacción 22:



Ejemplo 177

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-hidroxi-1H-indol-2-carboxílico.



El derivado de metoxilo del Ejemplo 1 (100 miligramos, 0.25 milimoles) se disuelve en 5 mililitros de DCM. Se agrega una solución de BBr_3 (1M en DCM, 2.5 mililitros, 2.5 milimoles), y la

524 526

mezcla se agita durante 18 horas. Luego se vierte sobre hielo, y se lava con EtOAc (30 mililitros). El pH de la capa de agua se ajusta a 9, y se extrae dos veces con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre sulfato de sodio anhidro, y se evaporan.

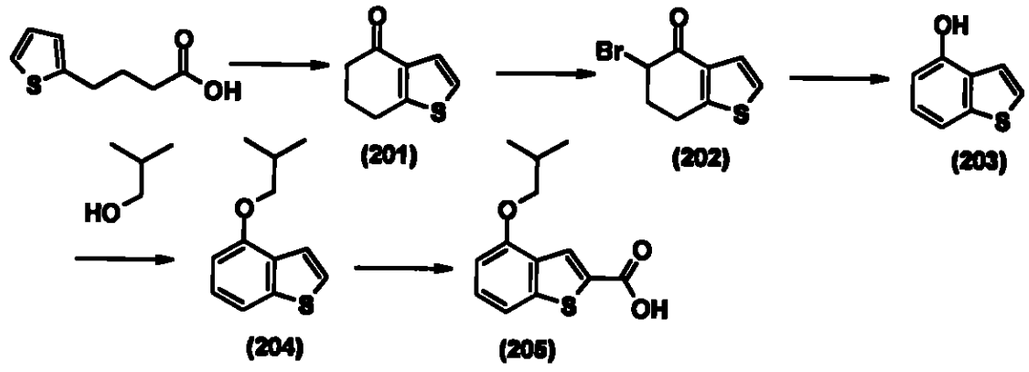
Rendimiento: 24 miligramos (25 por ciento).

MS (ESI): 385.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 9.62 (s, 1H), 8.14 (d, 1H), 7.2 (d, 1H), 6.94 (t, 1H), 6.86 (d, 1H), 6.37 (d, 1H), 3.75 (m, 1H), 2.89 (m, 2H), 2.53 - 2.65 (m, 6H), 2.39 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.47 - 1.68 (m, 10H), 1.25 (m, 1H).

Síntesis de las benzotiofen-2-carboxamidas

Los 4-alcoxi-benzotiofen-2-carboxilatos se sintetizan empezando a partir del ácido 4-tiofen-2-il-butírico (Esquema de Reacción 23).

Esquema de Reacción 2312:



525

(1) 6,7-dihidro-5H-benzo[b]tiofen-4-ona (198).

Se disuelve ácido orto-fosfórico (85 por ciento, 0.27 mililitros, 3.7 milimoles) en anhídrido de ácido acético (13 mililitros), y después de la adición de ácido 4-tiofeno-2-il-butírico (9 gramos, 52.9 milimoles), la mezcla se agita a 120°C durante 2.5 horas. La solución castaña se enfría empleando un baño de hielo, se agrega agua, y la mezcla de reacción se extrae con diclorometano. Las capas orgánicas se lavan con una solución de NaOH 2M, y dos veces con agua, hasta alcanzar un pH neutro. La solución se seca sobre Na_2SO_4, y se evapora bajo presión reducida. El producto crudo se obtiene como un aceite castaño (7.84 gramos), el cual se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, acetato de etilo / hexano, 9:1).

Rendimiento: 5.83 gramos (72 por ciento) de un sólido ligeramente amarillo. MS (ESI): 152 $[M]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.38 (d, 1H), 7.25 (d, 1H), 3.03 (t, 2H), 2.48 (m, 2H), 2.12 (t, 2H).

(2) 5-bromo-6,7-dihidro-5H-benzo[b]tiofen-4-ona (199).

Se disuelve 6,7-dihidro-5H-benzo[b]tiofen-4-ona (198, 5.8 gramos, 38.3 milimoles) en 200 mililitros de dietil-éter seco, y se enfría a -10°C. Se agrega lentamente una solución de bromo (6.1 gramos, 38.3 milimoles) en 30 mililitros de tetraclorometano y 2 a 3 gotas de dietil-éter. La mezcla se agita durante 15 minutos a -10°C, durante 15 minutos a 0°C, y 18 horas a temperatura ambiente. Luego se agregan lentamente agua y dietil-éter. Las capas orgánicas se lavan con agua, se secan sobre Na_2SO_4, y se evaporan.

526 526

Rendimiento: 8.7 gramos de un sólido amarillo (que contiene el 23 por ciento del material de partida). MS (ESI): 230, 232 $[M]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.46 (d, 1H), 7.3 (d, 1H), 4.87 (dt, 1H), 3.1 (m, 2H), 2.45 (m, 2H).

(3) Benzo[b]tiofen-4-ol (200).

Se colocan 5-bromo-6,7-dihidro-5H-benzo[b]tiofen-4-ona (199, 77 por ciento pura, 8.7 gramos, 28.9 milimoles), LiBr (5.7 gramos, 65.1 milimoles), y Li_2CO_3 (4.3 gramos, 57.8 milimoles) bajo argón en 300 mililitros de N,N-dimetil-formamida, y se ponen a reflujo durante 3 horas. La mezcla de reacción se deja enfriar a temperatura ambiente, y se evapora bajo un alto vacío. Después de la adición de agua helada y de una solución acuosa fría de HCl 2M, la mezcla se extrae con dietil-éter. Las capas orgánicas se extraen con NaOH 2M, y las capas acuosas combinadas se acidifican con HCl concentrado. El producto se extrae dos veces con acetato de etilo, y las capas orgánicas se lavan con una solución saturada de NaCl, se secan sobre Na_2SO_4, y se evaporan bajo presión reducida.

Rendimiento: 4.7 gramos de un sólido castaño, el cual se utiliza sin mayor purificación. MS (ESI): 149.0 $[M-H]^-$, 1H-RMN (DMSO-d_6): δ (ppm) 9.95 (br s, 1H), 7.55 (d, 1H), 7.45 (d, 1H), 7.38 (d, 1H), 7.15 (dd, 1H), 6.72 (d, 1H).

(4) 4-Isobutoxi-benzo[b]tiofeno (201).

Se disuelven benzo[b]tiofen-4-ol (200, 4.3 gramos, 28.9 milimoles) e iso-butanol (3.2 mililitros, 34.7 milimoles) bajo argón en 150 mililitros de tolueno. Después de la adición de trifenil-fosfina

(9.1 gramos, 34.7 milimoles) y de una solución de DEAD al 40 por ciento en tolueno (16.8 mililitros, 34.7 milimoles), la mezcla se agita a 120°C durante la noche. Después de enfriarse, la mezcla de reacción subsecuentemente se lava con una solución acuosa saturada de $NaHCO_3$ y una solución de NaCl, se seca sobre Na_2SO_4, y se evapora bajo presión reducida. Se remueve el óxido de trifenilfosfina mediante cristalización a partir de acetato de etilo y hexano, y el producto crudo se purifica adicionalmente mediante cromatografía por evaporación (gel de sílice, hexano / acetato de etilo, 9:1).

Rendimiento: 5.4 gramos (91 por ciento) de un aceite amarillo. MS (ESI): 206 $[M]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 7.62 (d, 1H), 7.5 (d, 1H), 7.44 (d, 1H), 7.27 (dd, 1H), 6.85 (d, 1H), 3.88 (d, 2H), 2.12 (m, 1H), 1.05 (d, 6H).

(5) Ácido 4-isobutoxi-benzo[b]tiofen-2-carboxílico (202).

Una solución 1.6 M de n-butil-litio en hexano (18 mililitros, 28.8 milimoles) se disuelve bajo una atmósfera de argón, en 100 mililitros de dietil-éter seco, seguido por la adición por goteo de una solución de 4-isobutoxi-benzo-[b]-tiofeno (201, 5.4 gramos, 26.1 milimoles) en 40 mililitros de dietil-éter. La mezcla de reacción se pone a reflujo durante 45 minutos, luego se enfría y se transfiere mediante una jeringa a una mezcla de hielo seco en exceso (115 gamos, 2.61 moles) en dietil-éter (el hielo seco se lava antes dos veces con dietil-éter). La mezcla se deja agitándose durante a la noche a temperatura ambiente, luego se distribuye entre dietil-éter y agua.

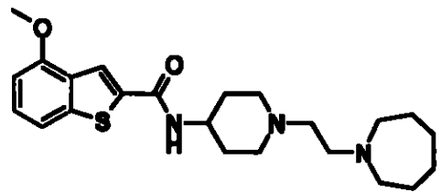
528 630

Las capas de éter se vuelven a extraer con agua. Las capas acuosas se acidifican con una solución acuosa de HCl 2M, y el precipitado se filtra, se lava con agua, y se seca bajo un alto vacío.

Rendimiento: 3.72 gramos (57 por ciento) de un sólido blanco. MS (ESI): 250 [M]+, 1H-RMN (DMSO-d_6): δ (ppm) 13.4 (br s, 1H), 7.98 (s, 1H), 7.55 (d, 1H), 7.43 (dd, 1H), 6.9 (d, 1H), 3.9 (d, 2H), 2.14 (m, 1H), 1.05 (d, 6H).

Ejemplo 178

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-benzo[b]tiofen-2-carboxílico.



Una solución de una mezcla de ácido 4- y 6-metoxi-benzo[b]tiofen-2-carboxílico (*C.R. Hebd. Seances Acad. Sci.* 1965, 261, 705) (440 miligramos, 1.05 milimoles), la amina 5 (357 miligramos, 1.05 milimoles) en 10 mililitros de N,N-dimetil-formamida, se trata con EDC (178 miligramos, 1.05 milimoles), hidrato de HOBT (178 miligramos, 1.15 milimoles), y trietil-amina (0.44 mililitros, 3.15 milimoles). La mezcla se agita durante la noche, y luego se evapora bajo un alto vacío. El residuo crudo se disuelve en acetato de etilo, y se lava dos veces con bicarbonato de sodio (10 por ciento), salmuera, y se seca sobre sulfato de sodio. Luego el producto crudo se purifica mediante cromatografía por evaporación

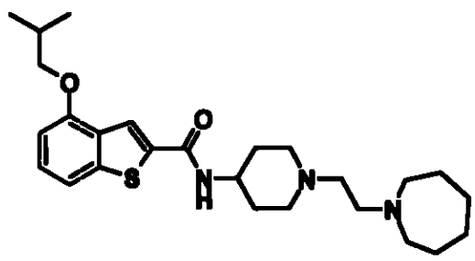
529 531

(acetato de etilo / metanol / amoníaco, 90:10:1).

Rendimiento: 45 miligramos (10 por ciento) de un sólido amarillo (y 84 miligramos del isómero 6-sustituido). MS (ESI): 416.1 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.53 (d, 1H), 8.2 (s, 1H), 7.5 (d, 1H), 7.37 (dd,1H), 6.9 (d, 1H), 3.94 (s, 3H), 3.7 (br m, 1H), 2.88 (m, 2H), 2.6 (m, 6H), 2.4 (m, 2H), 2.0 (m, 2H), 1.75 (m, 2H), 1.47 - 1.6 (m, 10H).

Ejemplo 179

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-benzo[b]tiofen-2-carboxílico.



Este compuesto se sintetiza a partir del compuesto 202 y la amina 5, de una manera análoga al método descrito en el Ejemplo 178.

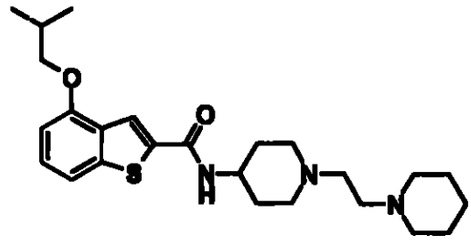
Rendimiento: 340 miligramos (53 por ciento) de un polvo beige. MS (ESI): 458.4 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.58 (d, 1H), 8.15 (s, 1H), 7.5 (d, 1H), 7.35 (dd, 1H), 6.88 (d, 1H), 3.9 (d, 2H), 3.7 (br m, 1H), 2.9 (m, 2H), 2.6 (m, 6H), 2.4 (m, 2H), 2.15 (m, 1H), 2.0 (m, 2H), 1.78 (m, 2H), 1.5 - 1.65 (m, 10H), 1.05 (d, 6H).

Ejemplo 180

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-

530 532

isobutoxi-benzo[b]tiofen-2-carboxílico.



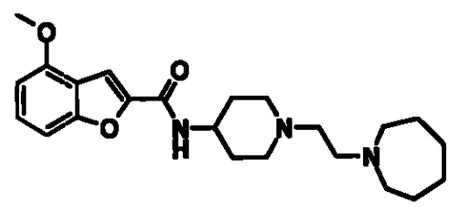
Este compuesto se sintetiza a partir del compuesto 202 y la amina 1, de una manera análoga al método descrito en el Ejemplo 178.

Rendimiento: 93 miligramos (26 por ciento) de un polvo beige. MS (ESI): 444.3 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.58 (d, 1H), 8.15 (s, 1H), 7.48 (d, 1H), 7.35 (dd, 1H), 6.88 (d, 1H), 3.9 (d, 2H), 3.7 (br m, 1H), 2.88 (m, 2H), 2.3 - 2.4 (m, 8H), 2.15 (m, 1H), 1.98 (m, 2H), 1.78 (m, 2H), 1.58 (m, 2H), 1.47 (m, 4H), 1.35 (m, 2H), 1.05 (d, 6H).

Síntesis de las benzofuran-2-carboxamidas

Ejemplo 181

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-benzofuran-2-carboxílico.



Este compuesto se sintetiza de una manera análoga al Ejemplo 1, a partir del ácido 4-metoxi-benzofuran-2-carboxílico y la amina 5.

MS (ESI): 400.2 $[M+H]^+$, 1H-RMN (DMSO-d_6): δ (ppm) 8.42 (d, 1H), 7.5 (s, 1H), 7.37 (t, 1H), 7.21 (d, 1H), 6.84 (d, 1H), 3.92 (s, 3H), 3.72

(m, 1H), 2.88 (m, 2H), 2.35 - 2.68 (m, 8H), 2.02 (m, 2H), 1.76 (m, 2H), 1.48 - 1.67 (m, 10H).

Los compuestos de la fórmula I en forma libre o en forma de sal farmacéuticamente aceptable, exhiben valiosas propiedades farmacológicas, por ejemplo como antagonistas de CCR2 y CCR5, como se indica en las pruebas *in vitro* descritas más adelante.

a) Ensayo de enlace de membrana CCR2.

Se emplea la tecnología SPA (Scintillation Proximity Assay - Ensayo de Proximidad de Cintilación) para demostrar que los compuestos de prueba impiden que la MCP-1 se enlace a las membranas celulares que expresan el receptor de CCR2. Se cultivan células CHO-dukX transfectadas que expresan establemente el gen hCCR2b, en un medio alfa MEM hasta una confluencia de entre el 70 y el 80 por ciento. Después de desechar el medio, se agregan 30 mililitros de una solución reguladora fisiológica helada que contiene EDTA 1 mM, y las células se remueven del plato utilizando un raspador. La suspensión celular se centrifuga a 800 g durante 10 minutos a 4°C, y el gránulo celular se vuelve a suspender en el regulador. Se hace la lisis celular utilizando un instrumento Polytron PTI300D a 28,000 revoluciones por minuto durante 30 segundos dos veces sobre hielo. Las membranas se recoléctan mediante centrifugación a 42,000 g durante 20 minutos a 4°C, y se someten a una segunda ronda de lisis (Polytron, 28,000 revoluciones por minuto, 30 segundos, dos veces, sobre hielo). En seguida de la centrifugación a 42,000 g durante 20 minutos a 4°C, las membranas

532 534

se vuelven a suspender en el regulador en una concentración de proteína de 2 miligramos / mililitro, y se almacenan a -80°C. Se preparan soluciones de suministro 10 mM de los compuestos de prueba en sulfóxido de dimetilo al 100 por ciento. Los compuestos de prueba se diluyen además en el regulador, para producir las soluciones concentradas cuatro veces, para las pruebas que ensayaron un intervalo de 10^{-10} a 10^{-5} M. El ensayo SPA se lleva a cabo en un volumen final de 200 microlitros por pozo en placas de 96 pozos. Los componentes se agregan, por pozo, en el siguiente orden:

50 microlitros de Regulador (+/- compuesto de prueba.

50 microlitros de perlas de aglutinina de germen de trigo-SPA (1.25 miligramos/pozo) en el regulador.

50 microlitros de suspensión de membrana CCR2B diluida con el regulador hasta 0.04 miligramos/mililitro (2 microgramos/pozo), alternativamente 50,000 células por pozo.

50 microlitros de [^{125}I]MCP-1 en el regulador (concentración final de 60 pM, 2.5 µCi/placa).

Después de la adición de todos los componentes, la placa se sella y se incuba durante 90 minutos a temperatura ambiente con agitación constante. En seguida de la incubación, la placa se centrifuga a 1000 revoluciones por minuto en un centrífugo Sorvall RC3B durante 4 minutos a temperatura ambiente, y se cuenta durante 3 minutos por pozo en un instrumento TOP COUNT (Packard). Se utilizan los conteos corregidos al apagarse, para el

533
535

análisis de enlace de radioligando.

Los compuestos de la fórmula I tienen una IC_{50} de entre 0.0003 y 10 µM.

De una manera similar, se han establecido ensayos de enlace para los receptores de CCR2 de rata, ratón, y mono Rhesus. Debido a la especificidad de las especies de los antagonistas de CCR2, los compuestos de la fórmula I tienen una IC_{50} de entre 0.015 y 10 µM sobre CCR2 de ratón, y de entre 0.020 y 10 µM sobre CCR2 de rata.

b) Ensayo funcional de CCR2 - Movilización de Ca2+

Células hCCR2b-CHO#84:

Se cultiva una línea celular CHOdukX que expresa establemente el gen hCCR2, en MEMα hasta una confluencia del 80 por ciento. El día anterior al del experimento, las células se cosechan desde el matraz de cultivo de tejido mediante tripsinización, se lavan, se aplican a una placa de 96 pozos de fondo negro/transparente a 5 x 10^4 células por pozo, y se cultivan durante la noche a 37°C en una atmósfera húmeda enriquecida con CO_2 al 5 por ciento. Al día siguiente, las células se lavan dos veces y se cargan durante 1 hora a temperatura ambiente en la oscuridad con Fluo-4 2 µM en el regulador C. Después de dos lavados adicionales, las células se vuelven a suspender en el regulador D. Las diluciones en serie de los compuestos, en el regulador D, se mezclan con las células, y se incuban durante media hora a temperatura ambiente en la oscuridad. Luego las células se estimulan mediante la inyección de MCP-1 y se monitorean los flujos de calcio utilizando el

534
856

Flexstation[MR], un fluorómetro de exploración de banco con una estación de trabajo de transferencia de fluido integrada.

	HBSS* 1X	Hepes 20mM	BSA al 0.1%	Probenecida 625µM	BSA al 0.5%
Regulador A	X	X			
Regulador B	X	X	X		
Regulador C	X	X		X	
Regulador D	X	X		X	X

* Solución alt balanceada de Hank (10X) sin rojo de fenol (#14065-049, Gibco BRL).

Células hCCR2b-300.19:

Se cultiva la línea celular Pre-B 300-19 que expresa establemente el gen hCCR2 (Loetscher y colaboradores, *J. Biol. Chem.* 276 (5), 2986-91 (2001)), en RPMI 1640 con glutamax-I complementado con aminoácido no esencial MEM 1X, piruvato de sodio 1 mM, ß-mercaptoetanol 5 x 10^{-5}, y suero fetal de becerro al 10 por ciento. Para el experimento, las células se utilizan en la fase de crecimiento exponencial, en una concentración máxima de 1.5 x 10^6 células por mililitro. Las células se lavan en el regulador A, y se cargan en aproximadamente 2.10^6 células por mililitro en fluo-4 2 µM en el regulador B durante 30 minutos en la oscuridad, a 37°C en un baño de agua. Después de dos lavados con el regulador A, las células se aplican a una placa de 96 pozos de fondo

535

negro/transparente, a 2 x 10^5 células por pozo en el regulador B. Todos los siguientes pasos, incluyendo al compuesto y las diluciones de quimiocina, se llevan a cabo como se describe anteriormente para las células hCCR2b-CHO#84, excepto que se utiliza el regulador B en lugar del regulador D.

En este ensayo, los compuestos de la fórmula I tienen una IC_{50} de entre 0.0005 y 10 µM.

c) Ensayo funcional de CCR2 - quimiotaxis.

Se utiliza un ensayo de migración celular *in vitro* para la quimiotaxis dependiente de CCR2 basado en insertos de membrana Transwell[MR], para perfilar los compuestos. El ensayo se lleva a cabo con la línea celular monocítica humana THP-1, y con linfocitos de sangre periférica activados (PBL). Las células THP-1 se cultivan en RPMI 1640 complementado con suero fetal de becerro inactivado por calor al 10 por ciento. Los linfocitos de sangre periférica activados se preparan a partir de sangre humana mediante elutriación, y luego se activan mediante cultivo sobre placas de cultivo recubiertas con CD3 anti-humano, y se expanden mediante un cultivo subsecuente en un medio complementado con IL-2. Se congelan alícuotas de linfocitos de sangre periférica activados, en nitrógeno líquido, y se utilizan en experimentos de migración después de descongelarse y de cultivarse durante la noche. Las células de los cultivos en una densidad de menos de 1.2 x 106 células/mililitro, se cuentan, se lavan, y se vuelven a suspender a una densidad apropiada en RPMI 1640 conteniendo albúmina de suero bovino al 0.5 por ciento. Se

536

utilizan insertos de membrana Transwell[MR] de 6.5 milímetros de diámetro, un tamaño de poros de 3 u 8 micras, y una membrana de policarbonato tratada con cultivo de tejido, para los ensayos de migración. Los insertos trans-pozos se cargan con células y compuestos en un volumen final de 100 microlitros en RPMI 1640 / albúmina de suero bovino al 0.5 por ciento. Para las células THP-1, se utilizan insertos con un tamaño de poros de 8 micras. Para los linfocitos de sangre periférica, el uso de insertos con un tamaño de poros de 3 micras dio como resultado conteos no específicos más bajos. Los insertos se colocan en una placa de cultivo de tejido de 24 pozos conteniendo MCP-1 humana recombinante y compuestos en un volumen final de 600 microlitros. Después de permitir que las células migren hasta el compartimiento del fondo, se detiene el ensayo removiendo y desechando los insertos trans-pozos. Las células del compartimiento del fondo se recolectan y se cuentan en un citómetro de flujo FACScan, adquiriendo todos los eventos durante 30 segundos, con las posiciones establecidas para cada tipo de célula. La migración se expresa como conteos celulares absolutos / 30 segundos, en relación con el número de células introducidas medido bajo las mismas condiciones.

En este ensayo, los compuestos de la fórmula I tienen una IC_{60} de entre 0.0012 y 10 μM.

<u>d) Ensayo de enlace de membrana CCR5.</u>

Se utiliza CCR5 humana para generar transfectantes estables en células CHO K1. Las membranas preparadas a partir de estos

537

transfectantes de CCR5, se utilizan en un ensayo de enlace de radioligando utilizando 125-I-MIP-1α como un ligando, y se prueban los compuestos de la fórmula I para determinar su actividad inhibidora. Los datos se reportan como IC_{50}, es decir, las concentración requerida del compuesto para alcanzar una inhibición del 50 por ciento del enlace de [I-125]MIP-1α.

Los Agentes de la Invención son efectivos como antagonistas dobles de CCR-2 y CCR-5. Por consiguiente, los Agentes de la Invención son útiles para la profilaxis y el tratamiento de enfermedades o condiciones médicas mediadas por CCR-2 y CCR-5. Las CCR-2 y CCR-5 tienen un papel importante en el tráfico de leucocitos, en particular en la migración de monocitos hacia los sitios inflamatorios, y pro consiguiente, los agentes de la invención se pueden utilizar para inhibir la migración de monocitos, por ejemplo, en el tratamiento de condiciones inflamatorias, alergias y condiciones alérgicas, enfermedades autoinmunes, dolor crónico, rechazo de injerto, cánceres que involucran filtración de leucocitos, estenosis o restenosis, ateroesclerosis, artritis reumatoide, osteoartritis, y dolor crónico.

Las enfermedades o condiciones que se pueden tratar con los Agentes de la Invención incluyen: Condiciones inflamatorias o alérgicas, incluyendo enfermedades alérgicas respiratorias tales como asma, rinitis alérgica, COPD, enfermedades de hipersensibilidad pulmonar, neumonitis de hipersensibilidad, enfermedad pulmonar intersticial (ILD), (por ejemplo, fibrosis

pulmonar idiopática, o ILD asociada con enfermedades autoinmunes tales como RA, SLE, etc.); enfermedad pulmonar obstructiva crónica, anafilaxis y respuestas de hipersensibilidad, alergias a fármacos (por ejemplo, a penicilinas o cefalosporinas), y alergias a picaduras de insectos; enfermedades inflamatorias del intestino, tales como enfermedad de Crohn y colitis ulcerativa; espondiloartropatías, esclerodoma; psoriasis y dermatosis inflamatorias tales como dermatitis, eczema, dermatitis atópica, dermatitis alérgica por contacto, urticaria; vasculitis;

enfermedades autoinmunes, en particular enfermedades autoinmunes con una etiología que incluya un componente inflamatorio, tales como artritis (por ejemplo, artritis reumatoide, artritis crónica progrediente, artritis psoriática y artritis deformans), y enfermedades reumáticas, incluyendo condiciones inflamatorias y enfermedades reumáticas que involucren pérdida ósea, dolor inflamatorio, hipersensibilidad (incluyendo tanto hipersensibilidad de las vías respiratorias como hipersensibilidad dérmica), y alergias. Las enfermedades autoinmunes específicas para las cuales se pueden emplear los Anticuerpos de la Invención incluyen desórdenes hematológicos autoinmunes (incluyendo, por ejemplo, anemia hemolítica, anemia aplástica, anemia de glóbulos rojos puros, y trombocitopenia idiopática), lupus eritematoso sistémico, policondritis, esclerodoma, granulomatosis de Wegener, dermatomiositis, hepatitis crónica activa, miastenia gravis, psoriasis, síndrome de Steven-Johnson, prurito idiopático, enfermedad

539

inflamatoria autoinmune del intestino (incluyendo, por ejemplo, colitis ulcerativa, enfermedad de Crohn, y Síndrome de Intestino Irritable), tiroiditis autoinmune, enfermedad de Behcet, oftalmopatía endócrina, enfermedad de Graves, sarcoidosis, esclerosis múltiple, cirrosis biliar primaria, diabetes juvenil (diabetes mellitus tipo I), uveitis (anterior y posterior), queratoconjuntivitis sicca y queratoconjuntivitis vernal, fibrosis pulmonar intersticial, y glomerulonefritis (con y sin síndrome nefrótico, por ejemplo incluyendo síndrome nefrótico idiopático o nefropatía de cambio mínimo);

rechazo de injerto (por ejemplo, en trasplante, incluyendo trasplantes de corazón, pulmón, corazón-pulmón combinados, hígado, riñón, páncreas, piel, o córnea), incluyendo rechazo de aloinjerto o rechazo de xenoinjerto, o enfermedad el injerto contra el huésped, y arterioesclerosis asociada con trasplante de órganos; ateroesclerosis;

cáncer con infiltración de leucocitos de la piel o de los órganos; cáncer de mama;

estenosis o restenosis de la vasculatura, en particular de las arterias, por ejemplo la arteria coronaria, incluyendo estenosis o restenosis que resulte de intervención vascular, así como hiperplasia neointima;

embolia;

y otras enfermedades o condiciones que involucren respuestas inflamatorias, incluyendo lesión por reperfusión, malignidades hematológicas, toxicidad inducida por citoquina (por ejemplo, choque

540
542

séptico o choque endotóxico), polimiositis, dermatomiositis, y enfermedades granulomatosas incluyendo sarcoidosis; enfermedades infecciosas, incluyendo VIH y SIDA.

Se debe entender que el término "tratamiento", como se utiliza en la presente, incluye tanto el modo terapéutico como profiláctico de terapia, por ejemplo en relación con el tratamiento de neoplasia, terapia para prevenir el establecimiento de neoplasia clínicamente o preclínicamente evidente, o para la prevención del inicio de células malignas, o para detener o revertir el progreso de células pre-malignas a malignas, así como la prevención o inhibición de crecimiento de neoplasia o metástasis. En este contexto, se debe entender que la presente invención abarca en particular el uso de los compuestos de la presente invención para inhibir o prevenir el desarrollo de cáncer de piel, por ejemplo carcinoma de células escamosas o basales a consecuencia de exposición a la luz ultravioleta, por ejemplo resultante de exposición crónica al sol.

Los Agentes de la Invención son particularmente útiles para el tratamiento de enfermedades del metabolismo de huesos y cartílagos, incluyendo osteoartritis y otros artrítidos inflamatorios, por ejemplo artritis reumatoide, y pérdida ósea en general, incluyendo pérdida ósea relacionada con la edad, y en particular enfermedad periodontal.

Los Agentes de la Invención también se pueden utilizar en aplicaciones oculares, las cuales incluyen el tratamiento de enfermedades oculares, en particular de desórdenes inflamatorios

541

oculares, de dolor ocular, incluyendo dolor asociado con cirugía ocular, tal como PRK o cirugía de cataratas, de alergia ocular, de fotofobia de diversa etiología, de presión intraocular elevada (en glaucoma) mediante la inhibición de la producción de la proteína de respuesta a glucocorticoides inducible por la malla trabecular (TIGR), y de enfermedad de ojo reseco.

Para las indicaciones anteriores, la dosificación apropiada, por supuesto, variará dependiendo, por ejemplo, del Agente de la Invención particular que se vaya a emplear, del sujeto que se vaya a tratar, del modo de administración, y de la naturaleza y severidad de la condición que se esté tratando. Sin embargo, en el uso profiláctico, en general se indica que se obtienen resultados satisfactorios en dosificaciones de aproximadamente 0.05 miligramos a aproximadamente 10 miligramos por kilogramo de peso corporal, más usualmente de aproximadamente 0.1 miligramos a aproximadamente 5 miligramos por kilogramo de peso corporal. La frecuencia de dosificación para el uso profiláctico normalmente estará en el intervalo de aproximadamente una vez por semana hasta aproximadamente una vez cada 3 meses, más usualmente en el intervalo de aproximadamente una vez cada 2 semanas hasta aproximadamente una vez cada 10 semanas, por ejemplo, una vez cada 4 u 8 semanas. El Agente de la Invención se administra de manera conveniente de una forma parenteral, intravenosa, por ejemplo en la vena antecubital u otra vena periférica, intramuscularmente, o subcutáneamente. Por ejemplo, un tratamiento

542

profiláctico normalmente comprende administrar el Agente de la Invención de una vez por mes a una vez dada 2 a 3 meses, o con menos frecuencia.

Los Agentes de la Invención se pueden administrar en combinación con otro agente activo. Los agentes activos adecuados incluyen antimetabolitos (por ejemplo, metotrexato), agentes anti-TNF (por ejemplo Remicade® (infliximab), Enbrel® (Etanercept), Humira® (adalumimab)), agentes anti-IL-1 (por ejemplo pralnacasan, ACZ885), inhibidores de transcriptasa inversa que son nucleósidos y que no son nucleósidos, inhibidores de proteasa de VIH, inhibidores de fusión y otros agentes anti-retrovirales. El agente o los agentes activos se pueden administrar de una forma simultánea, por separado, o en secuencia con el Agente de la Invención.

Las composiciones farmacéuticas de la invención se pueden fabricar de una manera convencional. Una composición de acuerdo con la invención de preferencia se proporciona en una forma liofilizada. Para la administración inmediata, se disuelve en un vehículo acuoso adecuado, por ejemplo agua estéril para inyección o suero fisiológico regulado estéril. Se considera recomendable formar una solución de un volumen mayor para administrarse mediante infusión, en lugar de hacerlo como una inyección de bolo, y es conveniente incorporar albúmina de suero humana o la propia sangre heparinizada del paciente en el suero en el momento de la formulación. La presencia de un exceso de esta proteína fisiológicamente inerte previene la pérdida del anticuerpo por

543
845

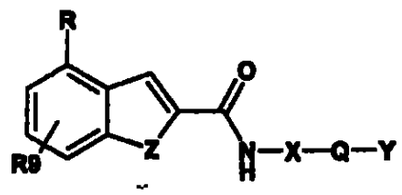
adsorción sobre las paredes del envase y la tubería utilizados con la solución para infusión. Si se utiliza albúmina, una concentración adecuada es del 0.5 al 4.5 por ciento en peso de la solución salina.

Los Agentes de la Invención se pueden administrar por cualquier vía convencional, por ejemplo oralmente, por ejemplo en la forma de soluciones para beber, tabletas o cápsulas, o parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables. Normalmente, para la administración sistémica se prefieren las formas de dosificación oral, aunque, para algunas indicaciones, los Agentes de la Invención también se pueden administrar tópicamente o dérmicamente, por ejemplo en la forma de una crema o gel dérmico o preparación similar, o, para los propósitos de aplicarse al ojo, en la forma de una crema ocular, gel, o preparación de gotas para los ojos; o se pueden administrar mediante inhalación, por ejemplo para el tratamiento de asma. Las formas de dosificación unitaria adecuadas para administración oral comprenden, por ejemplo, de 25 a 250 miligramos del Agente de la Invención por dosificación unitaria.

544

REIVINDICACIONES

1. Un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o éster de profármaco del mismo:



(I)

en donde:

Z es CR_1R_2, O ó S;

R se selecciona a partir del grupo que consiste en hidroxilo, un alcoxilo de 1 a 7 átomos de carbono opcionalmente sustituido, alquenoxilo de 2 a 7 átomos de carbono, ciclo-alquiloxilo, ariloxilo, heteroariloxilo, aril-alcoxilo de 1 a 7 átomos de carbono, o heteroaril-alcoxilo de 1 a 7 átomos de carbono, un alquilo de 1 a 7 átomos de carbono, o alquenilo de 2 a 7 átomos de carbono opcionalmente sustituido, un arilo opcionalmente sustituido, heteroarilo, o un grupo aril-alquilo de 1 a 7 átomos de carbono opcionalmente sustituido;

R9 representa uno o más sustituyentes de anillo seleccionados a partir del grupo que consiste en H, hidroxilo, un alcoxilo de 1 a 7 átomos de carbono opcionalmente sustituido, alquenoxilo de 2 a 7 átomos de carbono, cicloalquiloxilo, ariloxilo, heteroariloxilo, aril-alcoxilo de 1 a átomos de carbono o heteroaril-alcoxilo de 1 a 7 átomos de carbono, un alquilo de 1 a 7 átomos de

carbono o alquenilo de 2 a 7 átomos de carbono opcionalmente sustituidos, un arilo opcionalmente sustituido, heteroarilo, o un grupo aril-alquilo de 1 a 7 átomos de carbono opcionalmente sustituido;

R_1, R_2, y R_3 se seleccionan independientemente a partir del grupo que consiste en H y alquilo de 1 a 7 átomos de carbono;

X es cicloalquilo de 3 a 18, heterocicloalquilo, arilo, o heteroarilo, cada uno de los cuales puede estar opcionalmente sustituido;

Q es un enlazador de entre 1 y 3 átomos de longitud;

Y es cicloalquilo de 3 a 18 átomos de carbono, heterocicloalquilo, cicloalquilo puenteado, heterocicloalquilo puenteado, arilo, heteroarilo, arilo-heterocicloalquilo fusionados, todos los cuales están opcionalmente sustituidos de una manera independiente una vez o más;

el sustituyente o los sustituyentes opcionales sobre R y R9 se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo inferior-amino, aminocarbonilo, mono- ó di-alquilo inferior-aminocarbonilo, amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes, seleccionados a partir de grupo que consiste en

546

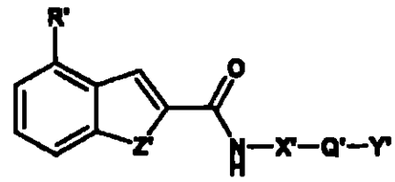
halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo;

el sustituyente o los sustituyentes opcionales sobre X se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo;

547

el sustituyente o los sustituyentes opcionales sobre Y se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo.

2. Un compuesto de la fórmula (II), o una sal farmacéuticamente aceptable, éster, o profármaco del mismo:



(II)

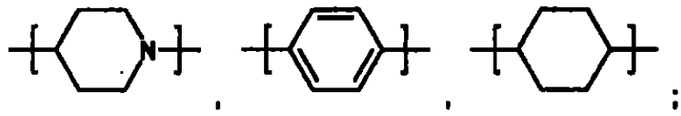
548
590

en donde:

Z' es NH, NCH_3, CH_2, S u O.

R' es hidroxilo, un alcoxilo de 1 a 7 átomos de carbono opcionalmente sustituido, alqueniloxilo de 2 a 7 átomos de carbono, cicloalquil-alquiloxilo de 1 a 7 átomos de carbono, ariloxilo, heteroariloxilo, heteroaril-alquiloxilo de 1 a 7 átomos de carbono, ó aril-alquiloxilo de 1 a 7 átomos de carbono, un arilo opcionalmente sustituido, heteroarilo, o un grupo aril-alquilo de 1 a 7 átomos de carbono opcionalmente sustituido;

X' se selecciona a partir del grupo que consiste en:



Q' se selecciona a partir del grupo que consiste en: $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-NH_2-$, $-CH(CH_3)-NH-$, $-CH_2-N(CH_3)-$, $-CH_2-CH(CH_2OH)-$, ó $-CH(CH_3)-NH(CH_3)-$;

Y' se selecciona a partir del grupo que consiste en: cicloalquilo de 3 a 18 átomos de carbono, heterocicloalquilo, cicloalquilo puenteado, heterocicloalquilo puenteado, arilo, heteroarilo, arilo-heterocicloalquilo fusionados, todos los cuales están opcionalmente sustituidos de una manera independiente una vez o más;

el sustituyente o los sustituyentes opcionales sobre R' se seleccionan independientemente a partir del grupo que consiste en

halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno, están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo;

el sustituyente o los sustituyentes opcionales sobre Y' se seleccionan independientemente a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo; todos los cuales, excepto halógeno,

550

están opcionalmente sustituidos de una manera independiente por uno o más sustituyentes seleccionados a partir del grupo que consiste en halógeno, hidroxilo, alquilo de 1 a 7 átomos de carbono, mono- ó di-alquilo de 1 a 7 átomos de carbono-amino, aminocarbonilo, mono- ó di-alquilo de 1 a 7 átomos de carbono-aminocarbonilo, amino, carboxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heterocicloalquilo de 3 a 18 átomos de carbono, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitrilo, arilo.

3. Un compuesto de acuerdo con cualquiera de las reivindicaciones anteriores, seleccionado a partir de:

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isopropoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isopropoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-[3S,4S)-4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclopropilmetoxi-1H-indol-2-carboxílico;

551

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(RS)-2-metil-piperidin-1-il]-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(4-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((2S,6R)-2,6-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((R)-3-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((S)-3-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-((1R,3S,5S)-3-hidroxi-8-aza-biciclo[32.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[4-(2-azepan-1-il-etil)-fenil]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

(4-{[metil-(tetrahidro-piran-4-il)-amino]-metil}-ciclohexil)-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

(4-{[metil-(tetrahidro-piran-4-il)-amino]-metil}-fenil)-amida del ácido

552

554

4-isobutoxi-1H-indol-2-carboxílico;

(4-{(R)-1-[metil-(tetrahidro-piran-4-il)-amino]-etil}-fenil)-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-(3-(R)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[2-((1R,3S,5S)-3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[8S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3-metil-butiloxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-ciclopentilmetoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(1,2-dimetil-propoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(2,2-dimetil-propoxi)-1H-indol-2-carboxílico;

553

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metil-pentiloxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,3-dimetil-butoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(furan-2-ilmetoxi)-1H-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4(furan-3-ilmetoxi)-1H-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il{-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benciloxi-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(5-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

554
886

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9Ar)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-

555

il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)-metil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3R,4R,5S)-4-hidroxi-3,5-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-

556

il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(7-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-ilmetil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-difluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il{-amida del ácido 4-(7-cloro-benzofuran-3-ilmetoxi)-1H-

indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-coro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3R,4R,5S)-4-hidroxi-3,5-dimetil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-1-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-

indol-2-carboxílico;

[1-(2-piperidin-1-il-metil)-piperidin-4-il]-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-.benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(7-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del

559

ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il]-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il-propil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4,6-dimetoxi-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

diclorhidrato de {1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5,6-dimetil-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[(S)-2-(4-hidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

561/563

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-fenoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico;

{1-[2-(3-(RS)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-m-toliloxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

{1-[2-(3-(RS)-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3-fluoro-fenoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3-fluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-fluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,4-difluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,5-difluoro-

562

fenoxi)-1H-indol-2-carboxílico;

{1-[2-(3-RS-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(3,5-difluoro-fenoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il}-amida del ácido 4-(6-cloro-piridin-2-iloxi)-1H-indol-2-carboxílico;

diclorhidrato de [1-(octahidro-quinolizin-1-ilmetil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(1-metil-piperidin-3-ilmetil)-piperidin-4-il]-amida del ácido 4-iobutoxi-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-((3R,4R)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4R,5S)-34-dihidroxi-5-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(R)-3-hidroxi-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-ciclobutilmetoxi-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3R,4R)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

563

[1-(octahidro-quinolizin-1-ilmetil)-piperidin-4-il]-amida del ácido 4-(2-metil-tiazol-4-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(3,4-dihidroxi-5-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-((3RS,4SR)-3,4-dihidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-fluoro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(S)-2-(3RS,4SR)-3,4-dihidroxi-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(9S,9aS)-1-(octahidro-pirido[2,1-c][1,4]oxazin-9-il)metil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(8S,8aS)-1-(hexahidro-pirrolo[2,1-c][1,4]oxazin-8-il)metil]-piperidin-4-il}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[(S)-2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-propil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

{1-[2-((3S,4S)-4-hidroxi-3-metil-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

{1-[(1S,9aR)-1-(octahidro-quinolizin-1-il)metil]-piperidin-4-il}-amida

569

del ácido 4-p-toliloxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-1S-metil-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-1R-metil-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[1-(2S-azepan-1-il-propil)-piperidin-4-il]-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2R-azepan-1-il-propil)-piperidin-4-il]-amida del ácido 4-(furan-3-ilmetoxi)-1H-indol-2-carboxílico;

{1-[2-(3,6-dihidro-2H-piridin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-azepan-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(3-amino-azepan-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

{1-[2-(3-fluoro-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-isobutoxi-1H-indol-2-carboxílico;

[4-(2-piperidin-1-il-etil)-fenil]-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

{4-[2-(4-hidroxi-piperidin-1-il)-etil]-fenil}-amida del ácido 4-(5-cloro-benzofuran-3-ilmetoxi)-1H-indol-2-carboxílico;

[1-(2-azepan-1il-etil)-piperidin-4-il]-amida del ácido 4-fenil-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-trifluorometil-fenil)-1H-indol-2-carboxílico;

565

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-p-tolil-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-dimetilamino-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benzo[12,5]oxadiazol-5-il-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3-ciano-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-[3-(3-metoxi-propoxi)-fenil]-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-trifluorometoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(2,4-dimetoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(3,4-dimetoxi-fenil)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-benzo[1,3]dioxol-5-il-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-piridin-4-il-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-(6-metoxi-

566

piridin-3-il)-1H-indol-2-carboxílico;

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-etoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(4-hidroxi-piperidin-1-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

{1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-(4-metoxi-fenil)-1H-indol-2-carboxílico;

{1-[2-(3-hidroxi-8-aza-biciclo[3.2.1]oct-8-il)-etil]-piperidin-4-il}-amida del ácido 4-(6-metoxi-piridin-3-il)-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-hidroxi-1H-indol-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-benzo[b]tiofen-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-benzo[b]tiofen-2-carboxílico;

[1-(2-piperidin-1-il-etil)-piperidin-4-il]-amida del ácido 4-isobutoxi-benzo[b]tiofen-2-carboxílico;

[1-(2-azepan-1-il-etil)-piperidin-4-il]-amida del ácido 4-metoxi-benzofuran-2-carboxílico.

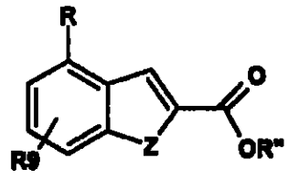
4. Un compuesto de acuerdo con cualquiera de las reivindicaciones anteriores, para utilizarse como un producto

farmacéutico para la prevención, reducción, o tratamiento de una enfermedad o condición autoinmune o inflamatoria.

5. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3 anteriores, para utilizarse como un producto farmacéutico para la prevención, reducción, o tratamiento de infección por VIH o SIDA.

6. Un proceso para la preparación de un compuesto de la fórmula (I), el cual comprende:

(a) hacer reaccionar un compuesto de la fórmula (III):

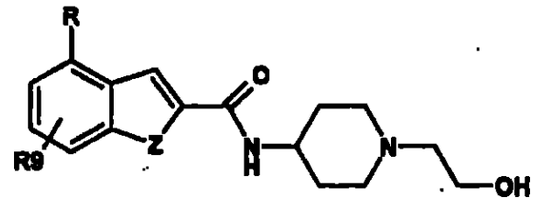


(III)

en donde R" es H o un grupo alquilo inferior, con un compuesto de la fórmula NH_2-X-Q-Y, siendo los grupos R, R9, Z, X, Q, e Y como se definen en la reivindicación 1; ó

(b) para la preparación de los compuestos de la fórmula (I) en donde X es piperidin-4-ilo y Q es -CH_2-CH_2-, e Y es un grupo que tiene la fórmula -NR_7R_8, en donde R_7 y R_8 están enlazados para definir colectivamente un heterocicloalquilo, cicloalquilo puenteado, heterocicloalquilo puenteado, heteroarilo, o arilo-heterocicloalquilo fusionados, hacer reaccionar un compuesto de la fórmula (IV):

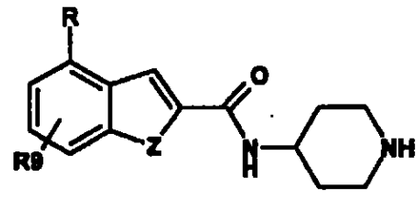
568



(IV)

con un compuesto de la fórmula NHR_7R_8, en donde R_7 y R_8 son como se definen anteriormente, y R, R9, y Z son como se definen anteriormente; ó

(c) para la preparación de compuestos de la fórmula (I), en donde X es piperidin-4-ilo y Q es CH_2-, hacer reaccionar un compuesto de la fórmula (V):



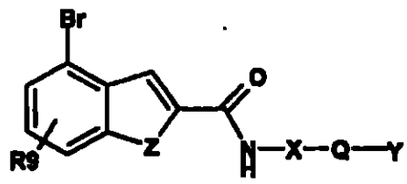
(V)

en donde R, R9 y Z son como se definen anteriormente, con un compuesto de la fórmula HO-CH_2-Y, en donde Y es como se define anteriormente; ó

(d) para la preparación de compuestos de la fórmula (I), en donde R es un grupo arilo opcionalmente sustituido, utilizar apropiadamente el grupo Br en un compuesto de la fórmula (VI) para

569

sustituir a este grupo arilo sustituido:



(VI)

en donde Z, R9, X, Q e Y son como se definen anteriormente;

y recuperar los compuestos resultantes de la fórmula (I) en forma libre o de sal.

7. Un compuesto que se puede obtener mediante el proceso de la reivindicación 5.

8. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, en asociación con un diluyente o vehículo farmacéuticamente aceptable.

9. El uso de un compuesto de acuerdo con la reivindicación 1, en la fabricación de un medicamento para utilizarse en el tratamiento de una enfermedad o condición autoinmune o inflamatoria.

10. El uso de un compuesto de acuerdo con la reivindicación 1, en la fabricación de un medicamento para utilizarse en el tratamiento de infección por VIH o SIDA.

11. Un método para inhibir los receptores de quimiocina o la proteína de macrófago, o para reducir la inflamación en un sujeto que necesite dicho tratamiento, cuyo método comprende administrar

570 571

a este sujeto una cantidad efectiva de un compuesto de acuerdo con la reivindicación 1.

12. Un método para el tratamiento de una enfermedad o condición inflamatoria o autoinmune, el cual comprende administrar a este sujeto una cantidad efectiva de un compuesto de acuerdo con la reivindicación 1.

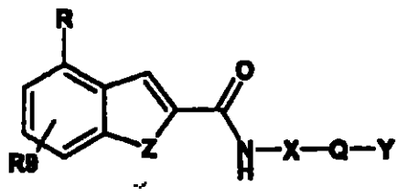
13. Un método para el tratamiento de infección por VIH o SIDA, el cual comprende administrar a este sujeto una cantidad efectiva de un compuesto de acuerdo con la reivindicación 1.

14. El uso de un compuesto de acuerdo con la reivindicación 1, en combinación con uno o más agentes seleccionados a partir de: metotrexato, un agente anti-TNF, un agente anti-IL-1, un inhibidor de transcriptasa inversa que es nucleósido o que no es nucleósido, un inhibidor de proteasa de VIH, un inhibidor de fusión, y un agente anti-retroviral para el tratamiento de una enfermedad o condición inflamatoria o autoinmune, o VIH o SIDA.

571

RESUMEN

Un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o éster de profármaco del mismo:



(I)

en donde las variantes R, R9, Z, X, Q, e Y se definen en la memoria descriptiva.

* * * * *

572

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.
PA/4-33647A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2005/001362	10/02/2005	11/02/2004
Applicant		
NOVARTIS AG		

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 the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [X] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

4. With regard to the title,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   [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

573

International Application No
PCT/EP2005/001362

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D405/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

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, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/32438 A (SMITHKLINE BEECHAM CORPORATION; WIDDOWSON, KATHERINE, L; NIE, HONG) 30 July 1998 (1998-07-30) claim 1	1-14
Y	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 20, 10 July 2001 (2001-07-10) & JP 2001 058988 A (TAKEDA CHEM IND LTD), 6 March 2001 (2001-03-06) abstract; claim 1	1-14

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

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 2005	16/08/2005

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	Wolf, C

3

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

574

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/001362

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.: 11-14
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATI NAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/001362

575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9832438 A	30-07-1998	AU 729893 B2	15-02-2001
		AU 5827898 A	18-08-1998
		BR 9807085 A	18-04-2000
		CA 2278427 A1	30-07-1998
		CN 1253501 A	17-05-2000
		EP 1005341 A1	07-06-2000
		HU 0001940 A2	29-01-2001
		JP 2002515055 T	21-05-2002
		NO 993585 A	21-09-1999
		NZ 336859 A	26-01-2001
		PL 334774 A1	13-03-2000
		TR 9901761 T2	21-10-1999
		WO 9832438 A1	30-07-1998
		US 5929250 A	27-07-1999
		US 6015908 A	18-01-2000
		US 6166055 A	26-12-2000
		US 6043374 A	28-03-2000
		ZA 9800519 A	23-10-1998
JP 2001058988 A	06-03-2001	AU 1690100 A	12-07-2000
		CA 2353635 A1	29-06-2000
		EP 1140896 A1	10-10-2001
		WO 0037455 A1	29-06-2000
		US 6235771 B1	22-05-2001

578 y 579
corresponden a tarjetas fraudulentas

576

Industria y Comercio
SUPERINTENDENCIA

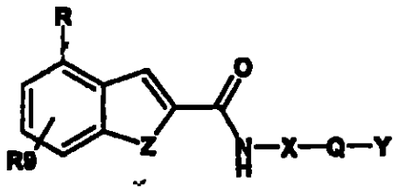
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int Cl: C07D 401/00
22) Fecha de solicitud:	(71)Solicitante(s) NOVARTIS AG
(30) Prioridad (31) *No. Prioridad* 32) *Fecha* (33) *País* 0403038.3 11/02/04 GB	(72) Inventor(es) RENE HERSPERGER PHILIPP JANSER EMIL PFENNINGER HANS JUERG WUETHRICH WOLFGANG MILTZ
	(74) Apoderado: CARLOS R. OLARTE
(85) Fecha límite inicio fase nacional: (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: *10/02/05* No. de solicitud *PCT/EP2005/001362*	(87) Publicación internacional Fecha: *25/08/05* N° publicación: *WO 2005/077932*

(54) Título: **ANTAGONISTAS DEL RECEPTOR DE QUIMIOCINA**

Resumen - Reivindicación(es):

Un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o éster de profármaco del mismo:



(I)

en donde las variantes R, R9, Z, X, Q, e Y se definen en la memoria descriptiva.

OLARTERAISBECK

1 577

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-078323- -00000-0000
Fec: 2006-08-09 17:30:36 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIVI
Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 580

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 11/09/06

SOLICITUD DE:

(4) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

SOLICITANTE (71)

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel, Suiza.
Nacionalidad o Domicilio: SUIZA
Lugar de Constitución: SUIZA
Teléfono: **Fax:**
E-mail:

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PÁGINA ADJUNTA Ver Folio 3
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2005/001362 Fecha Febrero 10, 2005

Publicación Internacional No. WO 2005/077932 Fecha Agosto 25, 2005

(54) **Título (54)** ANTAGONISTAS DEL RECEPTOR DE QUIMIOCINA

Clasificación Internacional (51) C07D 401/00 A61K 31/4709, A61P 31/18.

Prioridad
SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Febrero 11, 2004	0403038.3

(6) **Comprobante de pago No.** 06 – 58,179 **Fecha** Agosto 1, 2006

Industria y Comercio
SUPERINTENDENCIA

578
581

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-078323- -00000-0000
Fec: 2008-09-09 17:30:38 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEYII
Eve: 376 FASENACIONALI
Act 411 PRESENTACION Folios: 580

REQUISITOS MINIMOS PARA ADMISION PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [✓]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [✓] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

582

579

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO

REFERENCIA	Radicación No.	6 78323
	Solicitud internacional	EP2005/001362
	Fecha inicio fase nacional	11/09/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	11215

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.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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

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

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

El anterior requerimiento fue notificado por fijación en lista de fecha 06 OCT. 2006
aalvarado